

# Science & Technology

REVIEW

July/August 2003

National Nuclear  
Security Administration's  
Lawrence Livermore  
National Laboratory

## Customized Dose and Delivery of Cancer Radiotherapy

*Also in this issue:*

- Unexpected Effects of Low-Dose Ionizing Radiation on Cells
- Munitions with Controlled Lethality
- Livermore's New Decontamination and Waste Treatment Facility

## About the Cover

The lead article in this issue, which begins on p. 4, describes work by Livermore and University of California at Davis scientists to develop improved approaches to diagnose and treat cancer with more exactitude. The article describes ways in which cancer cells can be more accurately located and zapped with doses of radiation tailored to an individual's physiology. On the cover are images of radioisotopes in a patient's body. Radioisotopes taken internally have been used for many years as a diagnostic tool. Images such as the one on the left can be used in simulations to calculate the amount of radiation absorbed by the patient and where it is distributed in tumors and body organs.



Cover design: Kitty Madison

## About the Review

Lawrence Livermore National Laboratory is operated by the University of California for the Department of Energy's National Nuclear Security Administration. At Livermore, we focus science and technology on assuring our nation's security. We also apply that expertise to solve other important national problems in energy, bioscience, and the environment. *Science & Technology Review* is published 10 times a year to communicate, to a broad audience, the Laboratory's scientific and technological accomplishments in fulfilling its primary missions. The publication's goal is to help readers understand these accomplishments and appreciate their value to the individual citizen, the nation, and the world.

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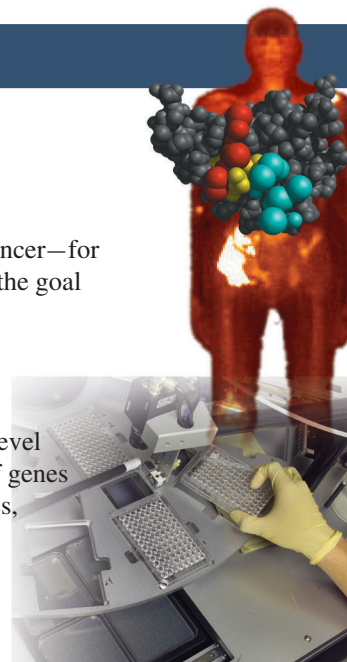
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### Anthrax virulence depends on the strain

Different strains of the bacterium that causes anthrax vary in their virulence, and scientists are beginning to understand why. Six scientists from Lawrence Livermore, Louisiana State University (LSU), and the U.S. Army Medical Research Institute of Infectious Diseases published findings in the *Journal of Clinical Microbiology* that could lead to more effective vaccines against anthrax and better tools for tracking the source of anthrax attacks. The paper's lead author was Pamala R. Coker, formerly of LSU and now at Livermore.

The anthrax genome has one large chromosome and two small pieces of DNA known as plasmids. The anthrax bacterium can contain not just one set of plasmids but could have as many as 243 copies of one plasmid and up to 32 copies of the other. That other plasmid, known as pX02, is more capable of causing disease when more copies of it are in a bacterial strain. In tests, the scientists found that an anthrax strain with just one pX02 plasmid killed 25 percent of the test animals, whereas a strain with 32 copies of the plasmid killed all the animals.

Scientists suspect the pX02 plasmid carries genes that allow the anthrax bacterium to develop an outer protein coat, and this coat shields it from the immune system. The more pX02 copies, the thicker that coating, and the more the anthrax bacterium can do its harm.

Coker says the discovery may help forensics scientists track down the country or laboratory that is the source of an anthrax strain used as a biological weapon. The plasmid technique could reveal genetic distinctions among varieties of anthrax, and that information could be used to match an attack germ with its terrorist perpetrator. She acknowledges that the research could also help others engineer more deadly forms of anthrax. Therefore, the federal government has urged scientists to carefully screen their work to prevent possible harm to national security. Livermore put the scientific paper through a careful security review before submitting it for publication.

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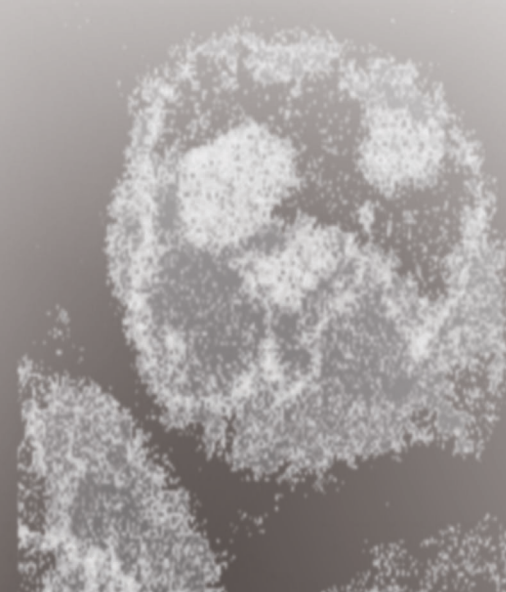
### Coming soon: more detection technologies

Scientists in Livermore's newly created Radiation Detection Center are investigating the application of more than a dozen advanced technologies to detect clandestine nuclear materials or nuclear devices. Many of the technologies were originally developed to search for black holes and supernovas in space. Now, these technologies contribute to fighting terrorism.

For example, Ultra-Spec is an ultrahigh resolution gamma-ray spectrometer that uses a detector at low temperatures to precisely measure gamma rays from nuclear materials. It records the warming caused by a single gamma ray hitting the detector's superconducting material (usually tin). The temperature increase is measured to a precision within 0.1 percent. Ultra-Spec users will be able to distinguish emissions from different types of radioactive materials, thereby allowing easier identification of the exact makeup of the materials.

Another example is the Gamma-Ray Imaging Spectrometer, one of five gamma-ray imaging systems under development. It permits large-area pictures to be taken of radioactivity emissions to determine the presence and location of radioactive materials. The gamma-ray camera consists of many gamma-ray sensors working together to take pictures, acting like a digital camera for gamma rays. The spectrometer is the size of a large-screen television and will provide a tenfold increase in sensitivity for detecting nuclear materials or devices.

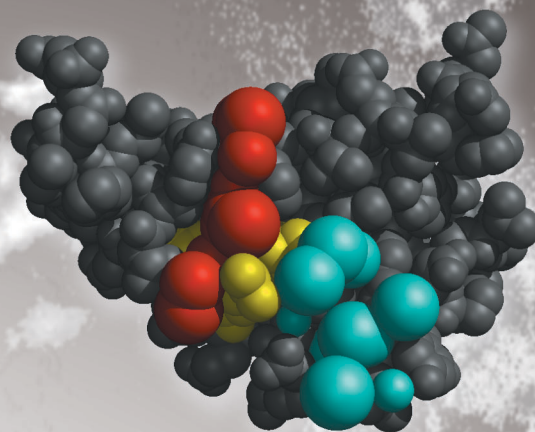
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## Calling All Nuclear Scientists



**E**XPERTISE in nuclear science, particularly in nuclear chemistry—the study of the inner workings of radioactive atomic nuclei—is at the heart of much of the research described in the article beginning on p. 4. Nuclear chemistry has been an area of scientific expertise at Livermore since the day the Laboratory was founded, when scientists needed to understand the behavior of fission and fusion products to design nuclear weapons. Today, weapons scientists put that understanding to work to maintain the country’s nuclear stockpile, using extremely large computers and laboratory experiments in the absence of full-scale underground testing.

We have a continuing need for well-trained nuclear chemists for stockpile stewardship, but universities are graduating very few of them these days. What’s a national laboratory to do? One solution is to train nuclear chemists ourselves, from a pool of capable young scientists we attract to the Laboratory.

Fascinating, state-of-the-art research projects, a few of which are described in this issue’s lead article, help draw prospective future nuclear chemists. Livermore chemists and others are designing molecules that can be tagged with a radioactive isotope to deliver deadly radiation straight to cancer cells that have spread throughout the body. A new detector under development uses the same radioisotope-tagged molecules to reveal the location of cancer cells. Meanwhile, scientists using a revolutionary type of mass spectrometry are witnessing, for the first time, how isotopes interact with human cells. Finally, Laboratory scientists are combining Livermore’s storehouse of data on nuclear science and radiation transport with the power of the supercomputer to create MINERVA, a tool for analyzing and planning targeted molecular radiation treatment for cancer patients. The development of MINERVA follows the successful commercialization of PEREGRINE, a similar hardware and software tool for planning radiation beam therapy.

Nuclear chemists are also contributing to programs in nonproliferation and homeland security to meet Laboratory

mission needs in a changing world. Scientists are being called on to detect tiny amounts of radiation and to manage the consequences of a radiological event.

The Laboratory has long been at the forefront in the development of many kinds of chemical, biological, and radiological detectors, both large and small, whether permanently installed or handheld. Today, two new handheld devices make use of entirely new technologies for detecting gamma radiation.

Laboratory scientists are also seeking ways to measure the body’s response to a small dose of radiation, as described in the article beginning on p. 12. With a better understanding of the effects of radiation on living tissue, medical personnel will be able to measure the dose received and intervene before individuals become sick and die. In effect, the human body would become a walking, talking dosimeter. The same collection of dosimetry data that has made PEREGRINE so successful in treating cancer with radiation beams is being brought to bear on this low-dose research.

With so much demand for nuclear chemists and so few university programs supplying them, Livermore must create its own experts. Helping to detect and cure cancer may seem far removed from keeping the nation’s nuclear stockpile safe and secure or responding to the demands of homeland security. In fact, the cancer research not only addresses an important national health issue but is also an effective tool for training nuclear chemists to confront national and worldwide security concerns.

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■ Tomas Diaz de la Rubia is associate director for Chemistry and Materials Science.



# An Inside Attack on Cancer

*Riding aboard  
new molecules  
synthesized at  
Livermore,  
radioisotopes can  
detect, diagnose,  
and treat cancer  
with unparalleled  
precision.*

**C**ANCER is always a dreaded diagnosis. Even with improvements in treatment results over the last few decades, cancer is still the second leading cause of death in this country.

Treatments for cancer include cutting, burning, and poisoning—surgery, radiation therapy, and chemotherapy—any combination of which is often highly successful in eradicating cancer cells. However, cancer that metastasizes, spreading to multiple sites in the body, has proved to be difficult to treat. Therapy with beams of radiation is only successful for localized cancers. At the same time, the 5-year survival rate for patients with detectable metastatic cancer who receive chemotherapy is less than 20 percent for many cancers.

Given that almost three-quarters of all cancer deaths involve cancers that have metastasized, finding an effective treatment method is a top national health priority. Livermore is facing this challenge head-on with a far-reaching set

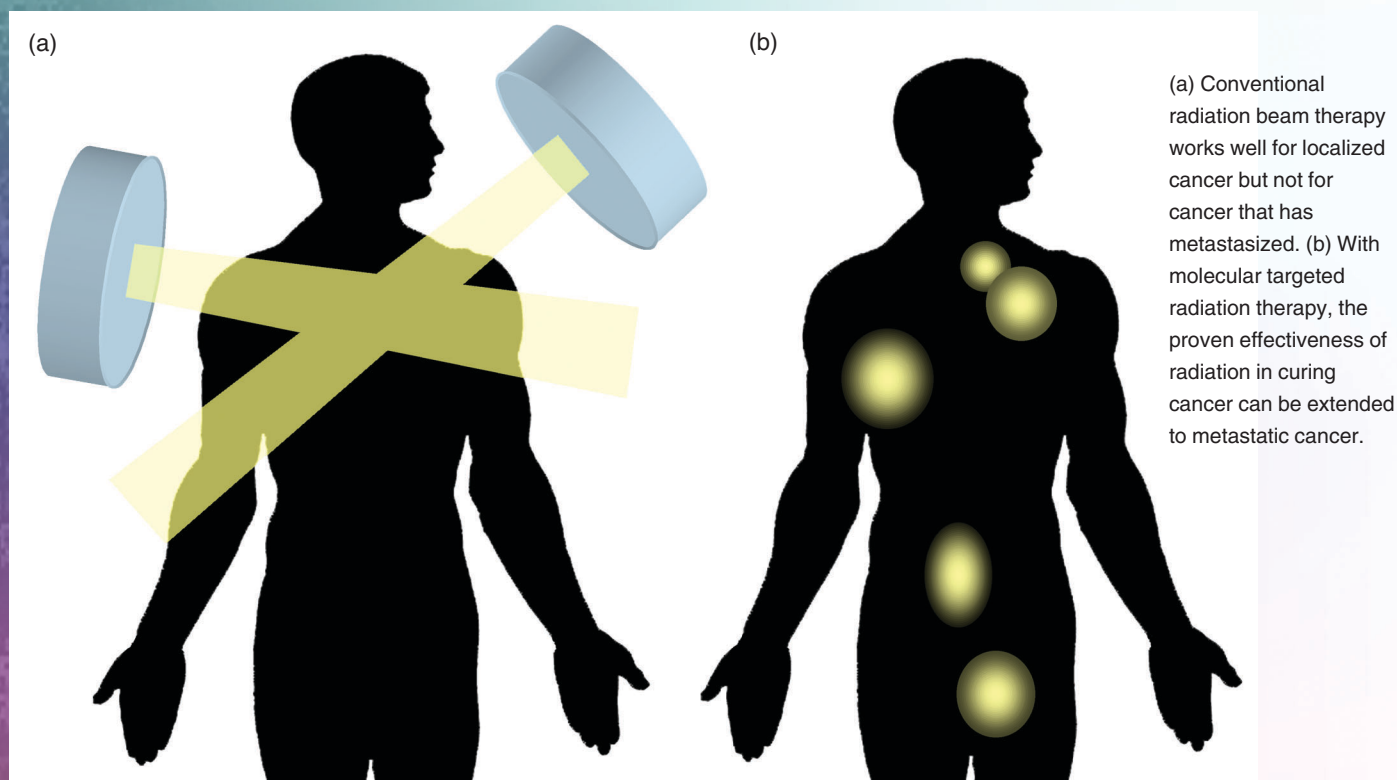
of projects overseen by medical physicist Christine Hartmann-Siantar, director of Livermore's Glenn T. Seaborg Institute. In pursuing this work, biochemists, computational biologists, material scientists, chemists, and physicists in two Livermore directorates—Chemistry and Materials Science and Biology and Biotechnology Research Program—are collaborating with scientists at the University of California (UC) at Davis Cancer Center.

Hartmann-Siantar had been principal investigator for development of PEREGRINE, a treatment planning program for radiation beam therapy that couples Livermore's storehouse of radiation transport data with powerful simulation tools and desktop computers. (See *S&TR*, May 1997, pp. 4–11; April 2001, pp. 15–17.) PEREGRINE, named for the patron saint of cancer patients, has since been commercialized and is now available to hospitals as a tool for accurately targeting cancer tumors with radiation beams.

“A couple of years ago, PEREGRINE was in the technology transfer phase, and the team was asking what we could do to save the next 100,000 cancer patients using radiation,” Hartmann-Siantar says. “Beam therapy cannot treat cancer that has metastasized. We wanted to know how we could address widespread cancer.”

At about the same time, Livermore and the UC Davis Cancer Center formed a research collaboration to fight cancer. In part as a result of that joint venture, the UC Davis Cancer Center was named a designated cancer center by the National Cancer Institute, one of the National Institutes of Health. Together, Livermore and UC Davis are seeking better ways to prevent, diagnose, and treat cancer.

This cancer-fighting initiative brought Hartmann-Siantar and others at Livermore together with many experts at the UC Davis Cancer Center, including physicians Sally and Gerald DeNardo, leaders of the Section of Radiodiagnosis and Therapy in the Molecular Cancer Institute at the UC





Davis Medical School. The DeNardos are pioneers in the treatment of cancers with radiation administered internally. They, together with Hartmann-Siantar and others at Livermore and UC Davis, envisioned much of the work that goes on today in four projects that are described here.

One team is perfecting a new way to get radiation inside the body and directed only at cancer cells. New molecules being synthesized in the laboratory will lock on to specific proteins, in a process known as molecular targeting. When the specially designed molecules are tagged with a radioactive isotope, deadly radiation can be delivered straight to cancer cells.

A problem with chemotherapy is that the toxicity it delivers to tumors is only slightly higher than what it delivers to healthy tissue. The beauty of targeted radionuclide therapy is that diseased cells receive a much higher fraction of drug. The radioactive material is busily destroying cancerous tissue while normal, healthy tissue stays healthy. This translates to no more nausea or hair loss for the patient.

Another team is developing a new imaging system that uses molecular

targeted radionuclides to reveal and diagnose breast cancer tumors. A third project is combining such images with computer software similar to PEREGRINE to make the planning of molecular targeted radiation therapy as specific to each patient as possible. Finally, a fourth project is using subcellular imaging to take snapshots that show how radioisotopes interact with cells to kill tumors.

Unfortunately, none of the systems currently under development will be available for patients in the immediate future. Says Hartmann-Siantar, "Even if we are wildly successful, it will be at least 10 and more likely 20 years before our advances mean widespread cures for metastatic cancer. After research and development are done, the phases 1, 2, and 3 trials take several years. That's just the way it works."

### Delivery System for the Cure

Because radiation is a proven killer of cancer cells, researchers have been searching for years for the best way to get radiation inside the body and directed specifically at tumors.

In 1985, a team led by the DeNardos was the first to use monoclonal antibodies

tagged with a radioisotope to treat cancer patients. Monoclonal antibodies are laboratory-produced substances that can locate and bind to cells wherever they are in the body. Many monoclonal antibodies are used in cancer detection or therapy; each one recognizes a different protein on certain cancer cells. Monoclonal antibodies can be used alone to stimulate the immune system, or they can be used as a system to directly deliver drugs, toxins, or radioactive material to a tumor. The first monoclonal antibodies were produced entirely from the cells of mice, which meant that rejection by the human body was common. In recent years, methods for "humanizing" monoclonal antibodies have greatly reduced the rejection rate.

Over the years, the DeNardos have treated more than 200 patients with radionuclide-tagged monoclonal antibodies for non-Hodgkin's lymphoma, prostate, and metastatic breast cancers. Lymphoma is a cancer of the lymphatic system, a network of thin vessels and nodes in the body whose function is to fight infection. Lymphoma is a particularly difficult cancer to treat because its tumors tend to be small and widespread. Cancers of the prostate and breast are carcinomas. Accounting for at least 80 percent of all cancers, carcinomas begin in the lining layer—epithelial cells—of organs.

The DeNardos' patients were typically at the end of the line, looking only to gain a few more months of life after not responding to conventional chemotherapy and radiation. Despite their grim prognosis, 60 percent of the patients responded to radionuclide-tagged antibody treatment, and 30 percent of that number have celebrated with complete remissions.

As internal radiation therapy for cancer was gaining ground in research hospitals, a project to develop synthetic antibodylike molecules began at

This diagram shows how a linker molecule will connect molecules that bind to two sites on a protein. When two molecules are connected with a linker, they bind with up to a million times higher affinity than does each molecule alone. The goal is to develop synthetic high-affinity ligands (SHALs) that bind to cancer cells. When tagged with a radioactive substance, the SHAL serves as a delivery system for cancer-killing treatment.



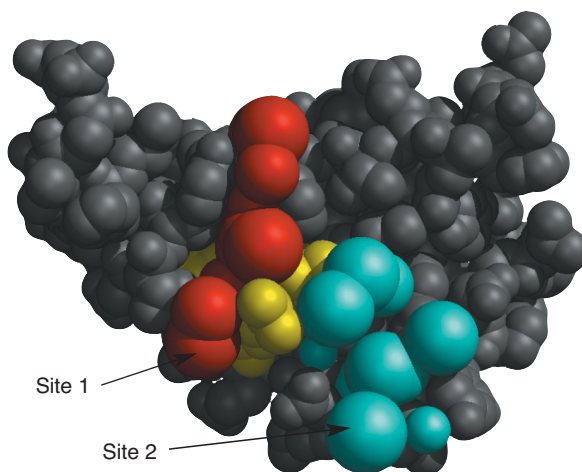
Livermore about three years ago. (See *S&TR*, June 2002, pp. 4–11.) The original goal for this work was to design molecules to bind to and capture proteins of biowarfare agents for fast, efficient detection. It was Gerald DeNardo who suggested to Livermore researchers that synthetic molecules could easily be tagged with radionuclides and used for cancer treatment.

Biochemist Rod Balhorn heads the team of biologists and chemists at Livermore who are producing the synthetic high-affinity ligands, or SHALs. The synthesis of a SHAL in the laboratory is the culmination of a process that integrates computations and experimental selection. A SHAL has two ends, each of which is a small molecule selected for its affinity to bind to a part of a particular protein (as determined through computational modeling by Felice Lightstone and other members of Mike Colvin's biomolecular modeling team). The two ends are combined by a linker molecule to create an entirely new molecule that will bind to the target protein thousands or even millions of times more strongly than either one of the original small molecules would have.

Livermore's first cancer-fighting SHAL, synthesized by Julie Perkins, binds to a receptor protein known as HLA-DR10 that is found on the surface of almost all non-Hodgkin's lymphoma cells. This SHAL, which will carry the radioactive isotope yttrium-90, is designed to rapidly pass through the liver and kidney to minimize the systemic damage that can occur when antibodies carry radionuclides.

"The new high-affinity ligands will have the selectivity of monoclonal antibodies without the 'baggage' that comes with antibodies," says DeNardo.

Initial laboratory testing of the non-Hodgkin's lymphoma SHAL at UC Davis will be to verify that it is selective for cancer. Researchers are examining



The first synthetic high-affinity ligand (SHAL) for cancer is designed to bind to HLA-DR10, a receptor protein found on the surface of almost all non-Hodgkin's lymphoma cells. The two sites on the HLA-DR10 molecule that the SHAL binds to were identified by Felice Lightstone.

the response of many kinds of tissue to the SHAL, using tissue arrays that have various types of healthy tissue—heart, liver, kidney, breast, and so on—as well as some cancerous tissue. The first SHAL tested has been shown to bind selectively to human lymphoma cells, and it doesn't bind to normal cells lacking the HLA-DR10 receptor. Future tests will use mice implanted with a human cancer to determine if the SHAL selectively localizes in the tumor, a feature critical for effective tumor targeting. The team will also be designing SHALs for prostate cancer and metastatic breast cancer in the next few years.

### Imaging to Detect

Radionuclide-tagged SHALs or monoclonal antibodies that bind tightly to cells can also serve as a diagnostic tool for cancer. The gamma rays they emit can be detected to reveal precisely where cancer cells are located. A team led by Livermore physicist Kai Vetter is developing a high-resolution gamma-ray imager designed to improve the odds of detecting breast cancer.

When a mammogram indicates the presence of a lesion in the breast, a biopsy must be performed. Yet 80 percent of such biopsies reveal a benign rather than a malignant lesion. Patients and doctors alike want to reduce the problem of false-

positive mammograms, reduce the need for invasive biopsies, make mammograms more sensitive, and generally improve breast cancer detection.

Today's gamma-ray detection systems can only detect lesions greater than about 10 millimeters across, which is too large to improve detection and treatment of breast cancer. Livermore's new technology is applying radiation detection systems developed for national security to the detection of breast cancer lesions just 1 to 2 millimeters in size.

Other isotope detection systems require that radiation emanating from the tumor source be aligned, or collimated. The new Livermore detector eliminates this need for collimation. Instead, it relies on recent developments in segmented semiconductor detectors and digital signal processing to measure the spatial distribution of the outgoing, tumor-based gamma rays. Because some gamma-ray energy is lost in the collimation process, eliminating collimation makes Livermore's new device just that much more efficient. Thus, technology advances have made it possible to realize the full potential of the gamma-ray imaging concept in the new detector.

An initial demonstration of Livermore's gamma-ray imager prototype will use small radioactive test lesions embedded in material designed to mimic the tissue of a woman's breast.

In developing the prototype, Vetter is working closely with UC Davis physicians and technical staff to optimize the imager's usefulness in a clinical setting.

### Imaging to Plan the Attack

The ability of targeted molecular radionuclides to locate tumors is being put to another use as well. By taking images of patients after they have received a small diagnostic radionuclide dose, physicians can determine exactly where the drug is distributed in the body. No other cancer treatment can provide that kind of dose information.

A team of researchers at Livermore, Montana State University, Idaho National Engineering and Environmental Laboratory (INEEL), and UC Davis is putting that dose data to work in new

treatment planning system known as Modality-Inclusive Environment for Radiotherapeutic Variable Analysis, or MINERVA. While the initial emphasis in the development of MINERVA is on targeted radionuclide therapy, the system can be used for any kind of external or internal radiotherapy or combination thereof.

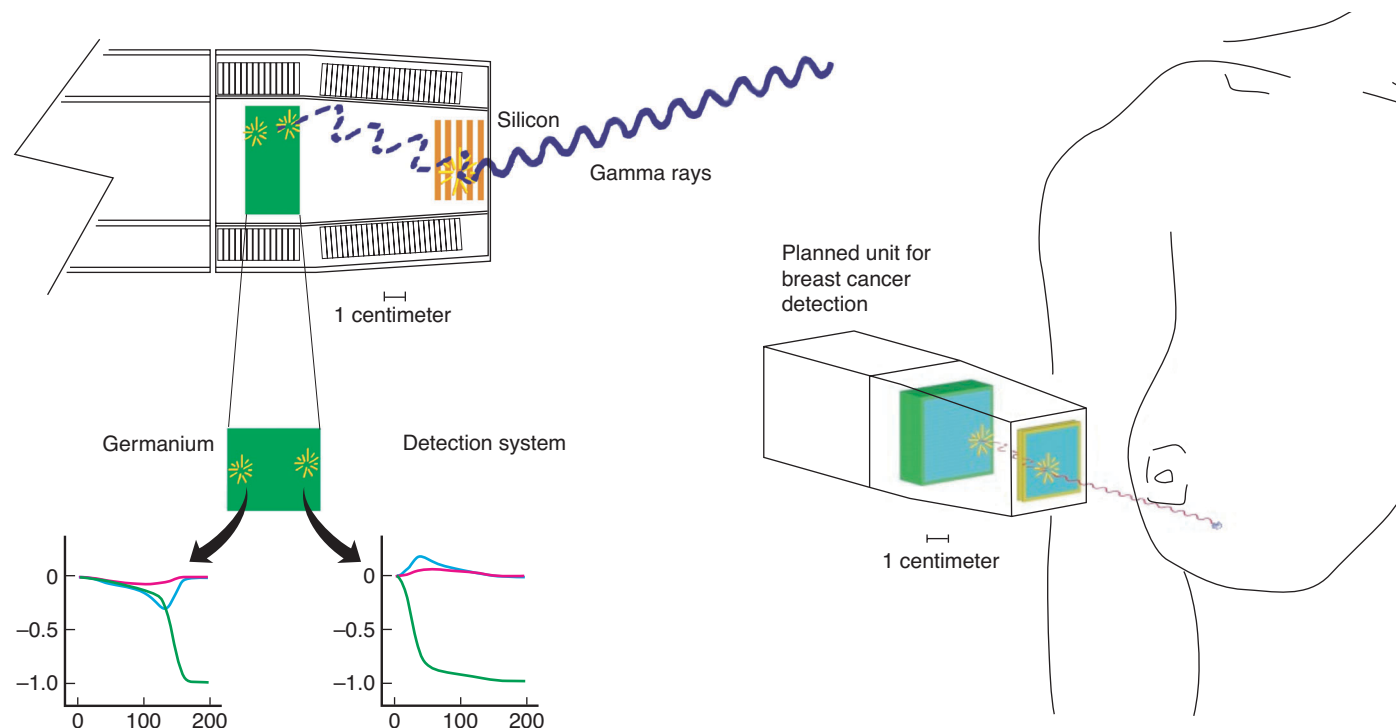
The team is making use of radiation-response data that have been accumulated over decades of conventional radiation beam therapy. They anticipate that this valuable data can be used to refine the estimates of what it will take to make targeted radiation therapy cure metastatic cancer while avoiding injury to healthy organs.

In MINERVA, INEEL's computational dosimetry system for neutron radiotherapy is being merged

with Livermore's fast, three-dimensional Monte Carlo PEREGRINE simulations for photon-electron therapy. Montana State is writing most of the user interface, and UC Davis is providing its expertise in targeted radiotherapy.

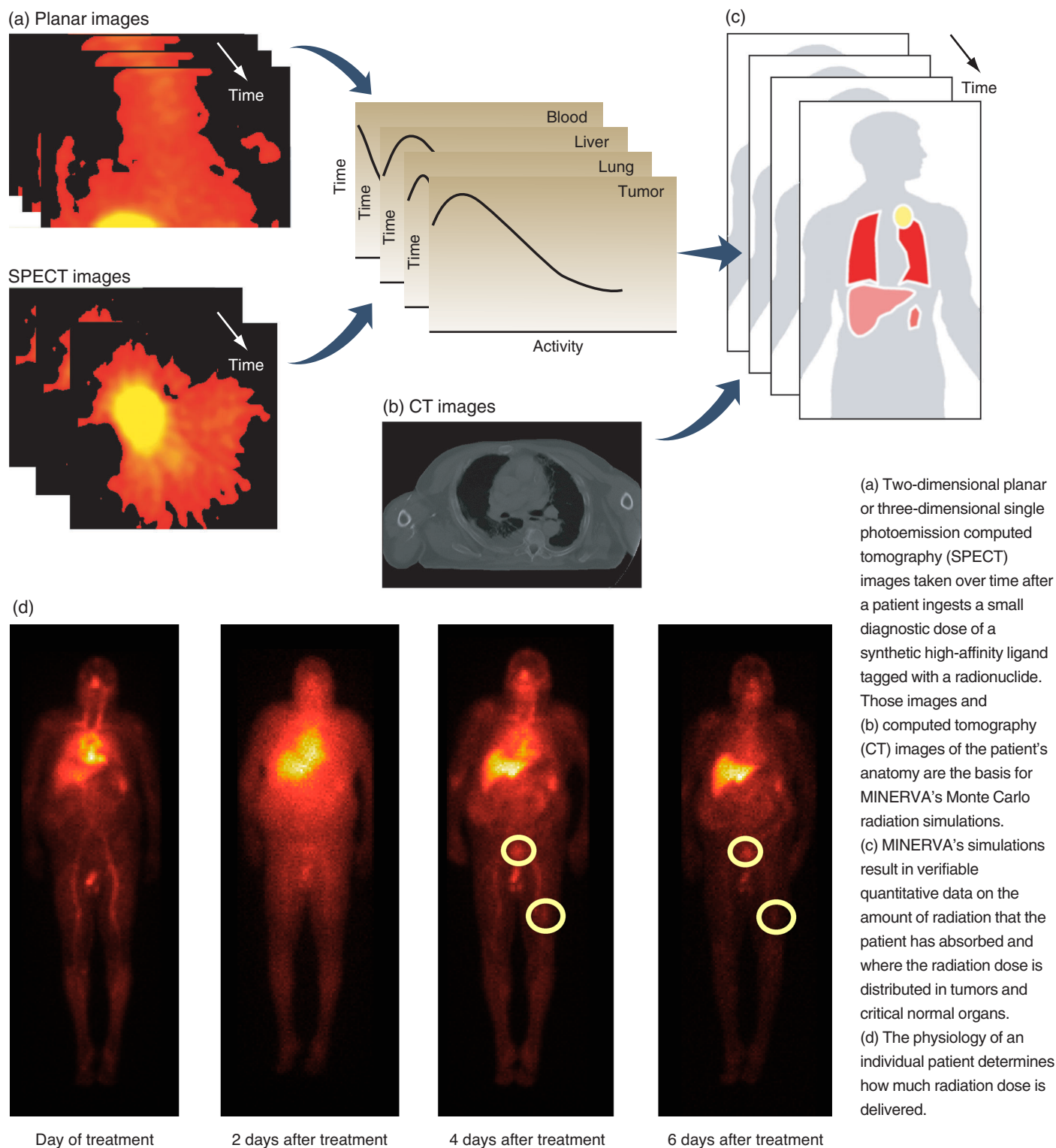
Says radiation physicist Joerg Lehmann, who directs Livermore's part of the effort, "Targeted radiotherapy has been in trials for many years and there are other planning programs around. But their dosimetry data are less accurate than MINERVA's will be."

Currently, dosimetry is based either on the patient's body surface alone or on risk assessment approaches used in diagnostic nuclear medicine. At the same time, treatment planning is not based on the patient's particular anatomy. The end result is that most patients are undertreated as doctors strive to avoid damage to normal



Livermore's new system for detecting breast cancer tumors relies on recent developments in segmented semiconductor detectors and digital signal processing. Unlike other gamma-ray detectors, this system does not require collimation (alignment) of the radiation emanating from the tumor source. Because some gamma-ray energy is lost in the collimation process, not requiring collimation increases system efficiency.





organs. No one wants the cure to kill the patient.

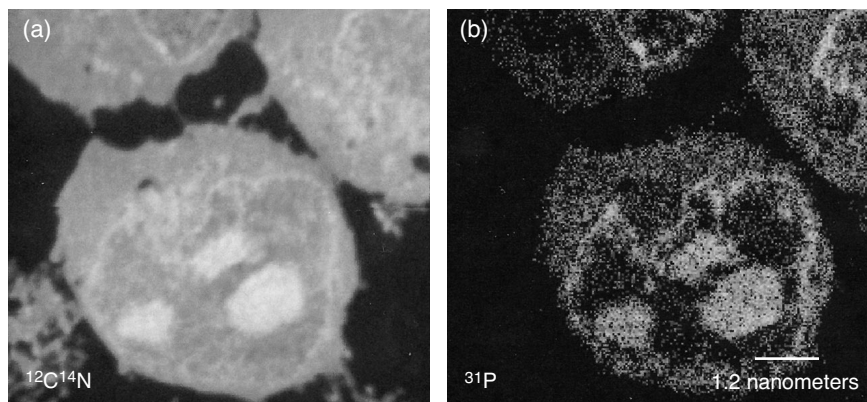
In contrast, MINERVA is designed to produce a customized treatment plan for each patient. When the system is up and running, it will reveal the time-dependent activity of radiation in the body. First, an initial test dose of

radiation in a SHAL or monoclonal antibody is administered to the patient. Then a series of images is taken of the radioisotope in the body over time using either two-dimensional planar images or three-dimensional single photoemission computed tomography (SPECT) images. The distribution of radiation activity in

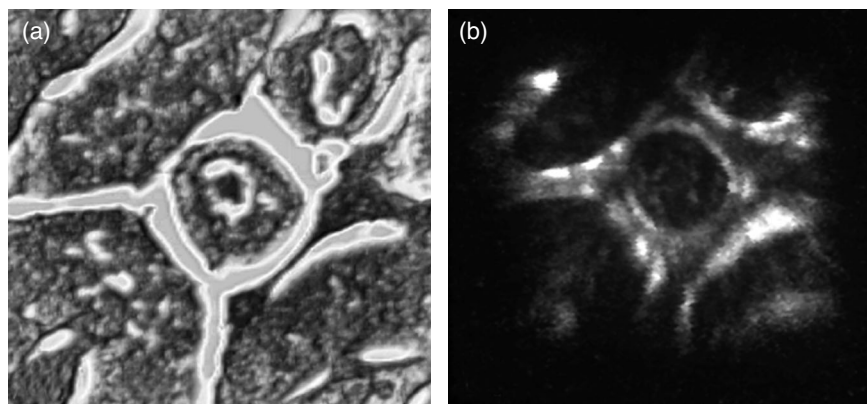
the body is based on these images and a set of computed tomography (CT) scans of the patient's body that show the location of organs. Monte Carlo radiation simulations will provide verifiable quantitative data on the amount of radiation that the patient has absorbed and where the radiation dose is distributed in tumors and critical normal organs.

Then comes decision time for the oncologist: Will this patient benefit from this kind of therapy? If so, how much dose should be administered to the particular patient?

At present, the resolution in available isotope imaging technologies is poorer than that of a CT scan. Isotope images also tend to be time-consuming to obtain. But as Livermore's collimatorless technology becomes available, the image and resolution will improve markedly, leading to even better data on the activity of the radiopharmaceutical.



Secondary ion images of Raji cells showing the distribution of (a) nitrogen (imaged as the  $^{12}\text{C}^{14}\text{N}$  ion) and (b) phosphorus ( $^{31}\text{P}$ ). These images were obtained with Livermore's new NanoSIMS and have a spatial resolution of approximately 50 nanometers. The ovoid-shaped bright regions in the center of the cell indicate nitrogen and phosphorus are concentrated in nucleoli. The membrane separating the cell nucleus is also clearly visible in the phosphorus image. The cell diameter is approximately 8 micrometers.



Two views of tubules in the cortex of an yttrium-treated mouse kidney. (a) Transmitted light photomicrograph. The tubule diameter is approximately 30 micrometers. (b) Secondary ion image showing the distribution of yttrium-89 in mouse kidney. Yttrium is not found in tubules but is concentrated in the spaces between tubules. The concentration of yttrium is highly variable from one tubule to another. Understanding how targeted radiopharmaceuticals—represented here by yttrium-89—are distributed in cells can lead to more effective cancer treatment.

## A Look Inside Cancer Cells

Once a tagged monoclonal antibody or SHAL attaches itself to a cancer cell, how does the radionuclide attack the cell and work its deadly magic? Researchers elsewhere have attached three different radioactive nuclides (iodine-131, copper-67, and yttrium-90) to Lym-1, a monoclonal antibody used to treat non-Hodgkin's lymphoma, with varying degrees of clinical effectiveness. The reasons for the differences in effectiveness are currently unknown.

To examine the specific effects radionuclides have on cells, a Livermore team recently began using a novel form of mass spectrometry with unprecedented spatial resolution to study the distribution of isotopes within individual cells. A goal is to determine the toxicities of various radioisotope-tagged molecules in both cancer and normal tissues and whether or not the localization of the drug can be correlated to its effectiveness.

In secondary-ion mass spectrometry (SIMS), ions with a few kiloelectronvolts

of energy bombard a solid sample in a vacuum chamber. In this process, called sputtering, surface atoms are ejected from the sample, ionized, and sent into a mass spectrometer for analysis. The secondary ions provide a direct measure of the elemental, isotopic, and molecular composition of the uppermost atomic layers of the sample's surface. SIMS has been used at Livermore for more than 17 years for high-precision analyses of many kinds of samples—weapons materials, radioactive waste to be stored at Yucca Mountain, meteorites, and even counterfeit money.

“About two years ago, we wanted to be able to characterize biological materials with SIMS,” says physicist Ian Hutcheon, who has been working with SIMS for 25 years. “But cells are very small, from 1 to 10 micrometers in size, and the spatial resolution with conventional SIMS wasn't good enough.”

So, Livermore purchased the NanoSIMS, a new instrument designed specifically for quantitative imaging of biological materials. Livermore's NanoSIMS, only the eighth instrument of its kind in the world, provides a spatial resolution of better than 50 nanometers, roughly 100 times better than that of conventional SIMS. The unit arrived in December 2002, and installation began in January. Although the NanoSIMS is not yet fully operational, the first studies have already provided a glimpse of cellular microstructure with remarkable clarity.

Well before the NanoSIMS was delivered, Hutcheon and his team began to develop procedures and standards for using SIMS on biological samples. Traditionally, SIMS has been used primarily on inorganic substances. Unlike inorganic materials, biological samples are largely water and behave badly in the high vacuum of a SIMS instrument. But Hutcheon's team overcame this problem by developing a biological sample-preparation technique

that removes the water while preserving the biochemistry and composition of the sample as well as its microstructure and morphology.

Using isotopically labeled monoclonal antibodies in both normal and cancer cells, the team began studying the distribution of yttrium-89 and iodine-127—stable surrogates for the radioisotopes often used in cancer therapy—in kidney, liver, and tumor samples of a mouse infected with lymphoma. The NanoSIMS images reveal for the first time just how yttrium-89 delivered by the molecule accumulates in a mouse's kidney. The yttrium is not found in the kidney tubules but rather is concentrated in spaces in between tubules. The images also show that the amount of yttrium is quite variable from one tubule to another. Data such as these offer great promise in understanding the toxic effect to the kidneys of different radionuclides. This examination of the cellular distribution of various molecular targeting radionuclides will help to determine the effectiveness of various radiopharmaceuticals in treating tumor cells as well as what, if any, effect that the pharmaceuticals have on normal organs.

“Using SIMS to examine biological samples is very new,” adds Hutcheon. “Our NanoSIMS is only the second one in the country with full-blown capabilities.”

### One Patient at a Time

Hartmann-Siantar expects that by the end of five years, phase 1 clinical trials of

Livermore's customized cancer-fighting SHALs will be under way while the collimatorless gamma-ray imaging device, MINERVA, and NanoSIMS will be in use in research settings.

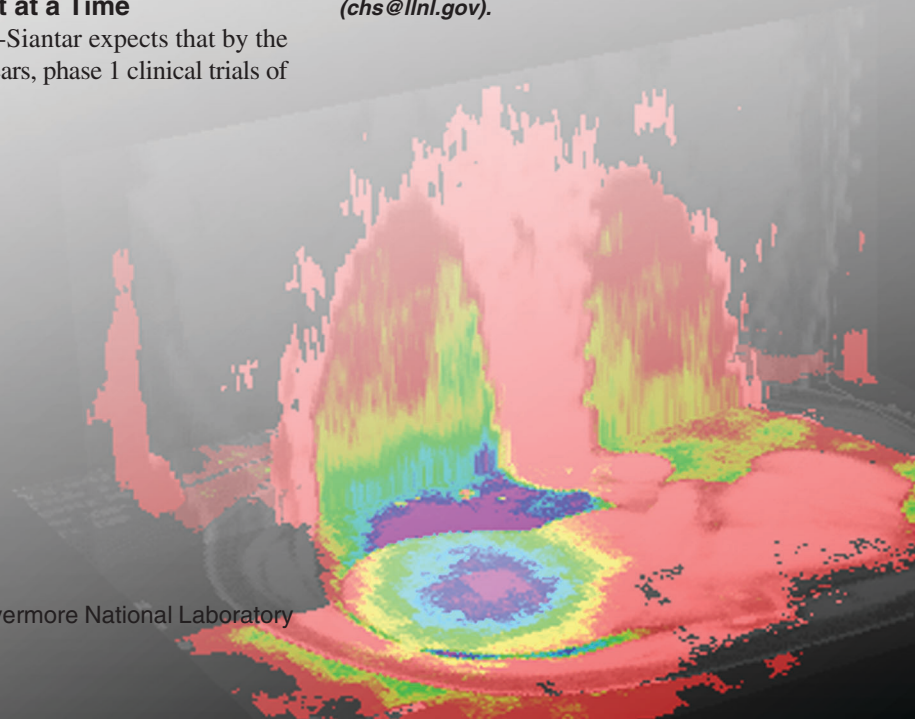
The high-resolution images from the collimatorless imager will begin to diagnose not only breast cancer but other cancers and diseases whose presence can be revealed with radioisotopes. MINERVA will be available to assist physicians in providing individualized treatment decisions, while the images from NanoSIMS will be offering cellular-level explanations for drug behavior in both mice and patients.

Because each of us is unique, one-size-fits-most medical treatments should not be the norm. In a more perfect world, we would be offered treatment options tailored to our own physiology. These new technologies are helping to bring that world a bit closer.

—Katie Walter

**Key Words:** gamma-ray detection, Modality-Inclusive Environment for Radiotherapeutic Variable Analysis (MINERVA), non-Hodgkin's lymphoma, PEREGRINE, radiation treatment, radiopharmaceuticals, secondary-ion mass spectrometry (SIMS), synthetic high-affinity ligand (SHAL).

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# Cells Respond Uniquely to Low-Dose Ionizing Radiation

*Research reveals that hundreds  
of genes help in coping with  
radiation's damaging effects.*



**F**OR decades, scientists have studied the cellular and genetic damage that follows exposure to high doses of ionizing radiation such as those resulting from nuclear accidents or cancer radiotherapy. Much less is known about cellular response to low doses of ionizing radiation—about 0.1 gray and below—such as that absorbed by our bodies during medical procedures and normal occupational exposures or while flying in an airplane. (See [box on p. 16](#).)

Research conducted by Lawrence Livermore scientists in the Biology and Biotechnology Research Program (BBRP) Directorate has revealed that cells exposed to low-level ionizing radiation respond in a surprisingly robust manner by turning on or off hundreds of genes, including those specialized in repairing damaged chromosomes, membranes, and proteins and countering cellular stress. These genes involved at low dose are different from the ones responding to high-dose radiation. The discovery that many different genes are called into action only in response to low-dose radiation suggests that a cell's response at low dose involves different functions than those occurring at higher doses.

The Livermore research is conducted on tissues of laboratory mice and human cell cultures. The mouse data show different baselines across tissues and specialized responses in irradiated brains. The research in human cells also reveals an intriguing adaptive response, whereby a very small pretreatment dose of ionizing radiation allows the cell to better withstand a later, much higher dose. Similar cellular damage responses may be at work when a cell suffers a low-level insult (injury) from harmful chemicals or is under attack by bacteria or viruses.

The Livermore research team is led by Andy Wyrobek, head of BBRP's Health Effects Genetics Division, and is

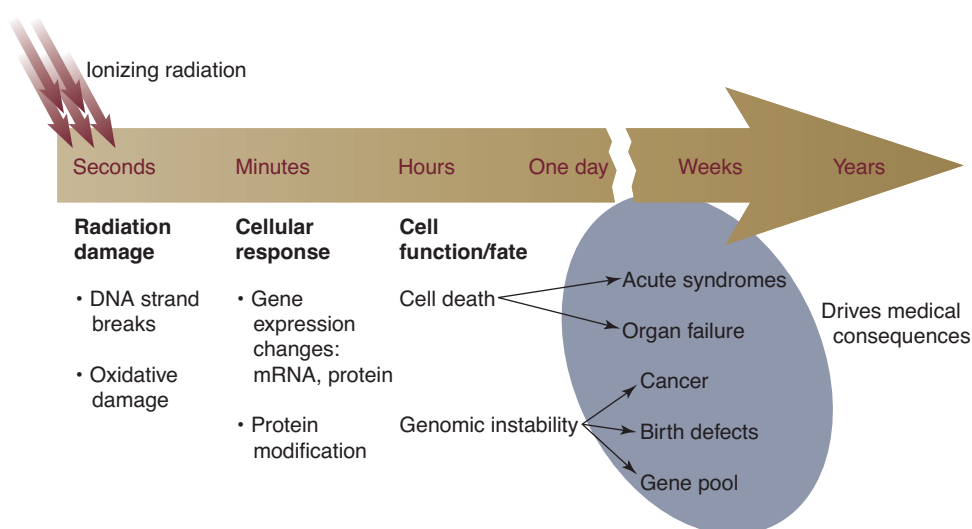
part of the Department of Energy's Low-Dose Radiation Research Program, which aims to understand the health risks of low-level radiation exposure. This understanding is critical to setting appropriate exposure standards, such as those for people receiving medical tests involving radioisotopes and workers who handle radioactive materials.

Since BBRP's inception in 1963, Livermore researchers have been studying the immediate and long-term health effects of radiation on cells, tissues, and individuals. Livermore-developed techniques, such as chromosome painting and the Glycophorin A and HPRT assays, have been used to monitor genetic damage in Japanese survivors of World War II atomic bomb blasts and in workers cleaning up the Chernobyl nuclear accident. (See *S&TR*, [September 1999](#), pp. 12–15.) Wyrobek says it is well-established that exposure to high doses

of ionizing radiation causes physiological, genetic, and chromosomal damage. This damage in turn can cause cell death and increase the risk for later diseases, including cancer and heritable mutations.

However, simply extrapolating from these effects at higher doses to predict changes in cells from low-dose exposure is problematic. Numerous assumptions have traditionally formed the basis for establishing low-level risk, despite the fact that scientists have been unable to directly demonstrate irrefutable health risks from low doses of ionizing radiation.

"We've used high-dose models because, until the past few years, we've been unable to detect cell changes following low doses of radiation," says Wyrobek. Thanks to advances in modern molecular biology and genome instrumentation, much of it developed under the Human Genome Program, this is changing. "We finally have the



An organism's response to ionizing radiation consists of a complex set of physical, chemical, and biological events. Within seconds, radiation produces damage to DNA and oxidizes proteins and DNA, lipids, and other biomolecules. Within minutes, the cell responds by changing the activation of certain genes and modifying some proteins. At high radiation doses, the result may be acute organ failure leading to death or genomic instability that causes cancer and birth defects and affects future generations.

tools to examine the damage response patterns in cells from low doses of ionizing radiation so that we can more scientifically determine health risks from low-dose exposures to ionizing radiation,” he says.

### Using Mice and Human Cells

To study low-dose cell responses, the researchers are examining the expression profiles of thousands of genes in tissues taken from irradiated adult mice and from irradiated human lymphoblastoid cells (derived from blood-forming cells). The mammalian brain is a relatively radioresistant tissue, while the small intestine and blood-forming tissues are the most sensitive. The team is comparing the findings to control groups of identical cells that received no radiation.

The mouse is an important animal model in radiation biology. Livermore researchers have studied its genome and found surprising similarities to the human genome. (See *S&TR*, May 2001, pp. 14–23.) Mice also provide researchers an opportunity to study many different organs.

The human lymphoblastoid cells were obtained from the National Institutes of Health, which supplies them to researchers nationwide. The cells,

originally taken from about 450 adults in the U.S. representing different ethnic backgrounds, are known to be sensitive to ionizing radiation.

Experiments were performed to study the effects of time and dose on gene expression in the mouse brain. A group of mice was irradiated with a 0.1-gray radiation dose from a cesium-137 source, and brain tissue was taken for analysis at 30 minutes and at 4 hours after irradiation. A second mouse group was irradiated with a 2-gray dose (20 times the low-dose radiation and enough to kill some cells), and tissue was sampled 30 minutes and 4 hours later. The same experimental procedure was used for the human lymphoblastoid tissue cells.

The team knew that at higher doses and possibly at low doses of radiation, some genes would respond by modulating their gene expression; that is, they would show either an increase or decrease in messenger RNA (mRNA) or protein levels. (In gene expression, the gene’s coded information is converted into mRNA and proteins that are required for cell function and structure.) The researchers examined the populations of mRNA and proteins present in irradiated cells and compared them to mRNA and proteins present in

nonirradiated cells as a means to determine whether genes had modulated.

### Microarrays Are Key

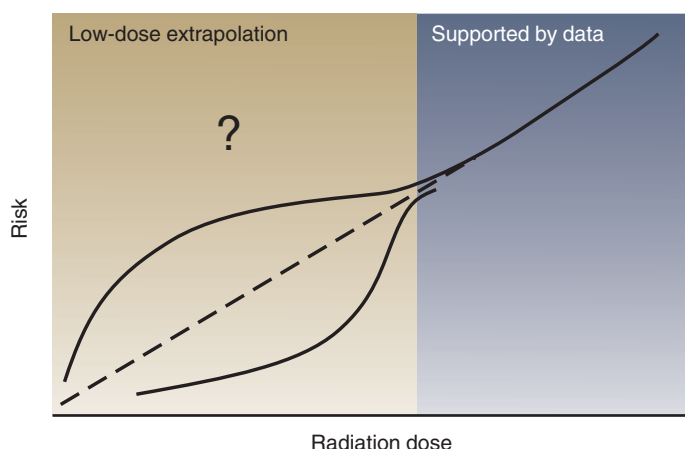
To simultaneously examine the response of tens of thousands of genes, the team turned to gene-transcript (mRNA) microarray technology, which uses slides or chips containing arrays of up to 20,000 different genes (specific sequences of DNA). The team used both Livermore-manufactured DNA microarrays and commercially available versions.

“Microarray technology allows us to take a nearly global view of what happens to a large number of genes in a cell. It replaces the single-gene approach used in the past,” says Wyrobek. He explains that the technology involves labeling pieces of DNA with fluorescent molecules and hybridizing (pairing) them to their complementary DNA target. Much of the fluorescence hybridization technology was pioneered at Livermore and then transferred to private industry.

Following the irradiation step, the team extracted the mRNA from the brain cells, converted it to its complementary DNA (cDNA), labeled that with a fluorescent dye, and applied the fluid mixture to a microarray. The different molecules of cDNA in solution paired with their corresponding genes on the array. The same procedure was done to a control group of cells.

Explains BBRP biomedical scientist Francesco Marchetti, “We can label cDNA from an irradiated cell red and label cDNA from a normal cell green. If we see equal amounts of both red and green for a particular gene, then we know that radiation causes no modulation of that gene. By the same logic, if we see all green, then that particular gene is shut down by radiation. If we see all red, then radiation has switched on that

Scientists have been unable to directly demonstrate irrefutable health risks from low doses of ionizing radiation. As a result, they have made numerous assumptions for establishing the risk.





gene. So the color shifts at each spot on the slide give us information on up to 20,000 genes or more.”

Analysis of the microarray generates large volumes of data that require advanced biostatistical and bioinformatics methods. “Fortunately, Livermore is the right place to do these kinds of data-intensive experiments,” biomedical scientist Matt Coleman says.

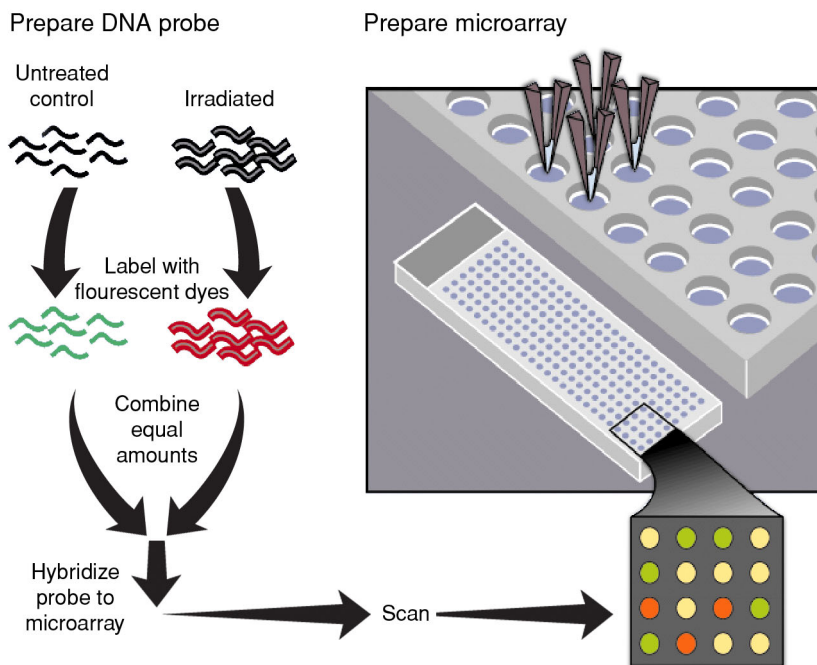
The microarray data are beginning to answer several basic questions the team posed prior to the beginning of the project: Are there genes with differential expression after radiation exposure? Is 0.1 gray enough to elicit gene expression changes in the adult mouse brain? What are the cell functions associated with genes affected by ionizing radiation?

### Genes Unique to Low Dose

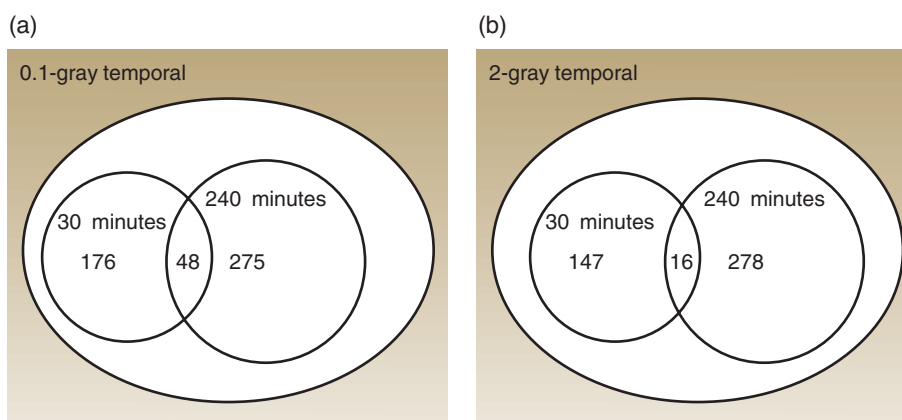
One of the most important findings from the microarray experiments is that cells exposed to a 0.1-gray radiation dose modulate different genes than cells exposed to a 2-gray dose. Likewise, there are also changes over time after exposure; different genes are modulated at 30 minutes and at 4 hours.

The results of one set of experiments involving mice brain cells showed that at a 0.1-gray dose, 176 genes were modulated at 30 minutes and 275 genes were modulated at 4 hours. An overlapping set of 48 genes was time-independent. The genes that are switched on are called REOS genes, or radiation-induced early-onset (within minutes to hours after exposure) and sensitive genes. At a 2-gray dose, 147 genes were modulated at 30 minutes and 278 genes were modulated at 4 hours, with 16 genes being time-independent.

A big surprise was the robust response of cells to ionizing radiation of only 0.1 gray. Says Wyrobek, “When I started this project, I thought we would see very few changes, if any, from such a low dose.



Microarray technology allows the simultaneous examination of tens of thousands of genes through the use of slides or chips. The technology involves extracting all messenger RNA from the irradiated cells, converting it to its complementary DNA, labeling it with a fluorescent dye, and applying it to a microarray. The different molecules of DNA attach to their corresponding genes. The same procedure is done to a control group of cells, but with a different color of fluorescent dye. A laser scans the microarray and analyzes the intensity of the different colors to give information on each gene.



(a) The results of one set of experiments involving mice brain cells showed that at 0.1 gray, 176 genes were modulated (produced more or less messenger RNA) at 30 minutes and 275 genes were modulated at 4 hours. An overlapping set of 48 genes was time-independent.

(b) At 2 grays, 147 genes were modulated at 30 minutes, 278 genes were modulated at 4 hours, and 16 genes were time-independent.

“The experiments show that the low-dose response is not simply less than a high-dose response. It’s a lot more complicated than that. What is happening here is not linear. For the low-dose extrapolation to be linear, the lower dose would be expected to show less of an effect on expression than the higher dose. But we found many genes where something is uniquely happening in response to low dose—a unique set of genes is getting turned on.”

For the mouse brain cells, the genes that modulated exclusively at 0.1-gray

appear to be involved in a broad variety of cell functions, including cell-cycle control; DNA, RNA, and protein synthesis and repair; fatty acid metabolism; heat shock; ion regulation; stress response; membrane repair; and myelin (material surrounding nerve fiber) repair. “The list of these pathways suggests that low-dose ionizing radiation may activate protective and repair mechanisms,” says biomedical researcher Eric Yin. He notes that low-dose radiation also depresses genes associated with brain signaling activity,

probably to divert more resources to repair functions.

The general findings for mouse cells were also seen in the human lymphoblastoid cells, both at the 0.1-gray and 2-gray dose levels. The human tissue cells showed a different set of genes for low-dose response, as might be expected because the cells examined were not brain cells. Wyrobek says it is too early to compare the numbers of genes and the pathways involved between the two kinds of cells because comparable microarrays are not yet commercially available.

## Ionizing Radiation: A Short Primer

The broad term radiation includes light and radio waves, but it is often used to mean ionizing radiation. Ionizing radiation has sufficient energy to remove electrons from atoms, thereby creating charged particles (ions or radicals) in materials it strikes. The different kinds of ionizing radiation include neutrons and alpha, beta, gamma, and x radiation. Atoms that emit any of these types of ionizing radiation are radioactive.

The international standard unit of an absorbed dose of ionizing radiation is the gray. One gray is equivalent to the absorption of 1 joule of energy per kilogram of material. It also equals 100 radiation absorbed doses (rads) in the old radiation measuring system. A hundredth of a gray, or one centigray, equals one rad.

Background ionizing radiation levels measure about 0.37 centigray per year, consisting of about 0.3 centigray from natural sources and about 0.07 centigray from sources of human activity. Sources of natural ionizing radiation include radon gas, the human body, rocks and soil, and cosmic rays. Sources of human-caused ionizing radiation include medical procedures, consumer products, and, to a lesser extent, airplane travel, color television, atmospheric fallout from old nuclear tests, and the nuclear power industry.

The occupational exposure limits to ionizing radiation are 5 centigrays per year. Patients undergoing radiation therapy typically receive a daily dose of about 2 grays, with a total dose of about 50 grays or more.

Exposure to large amounts of ionizing radiation can increase the risk of cancer and genetic mutations that can be passed on to future generations. If the dose is large enough, massive cell death can occur as part of acute radiation sickness, which can lead to death. The extent of cell damage depends on the total amount of energy absorbed, the time period and dose rate of exposure, and the particular organs exposed.

Determining exposure limits for workers is an important task for the Department of Energy and other federal agencies. The goal of DOE’s Low-Dose Radiation Research Program is to help determine health risks from exposures to low levels of radiation. This information is critical to adequately and appropriately protect people, especially those who are exposed to low levels of ionizing radiation on the job.

Over the next century, experts predict that radiation exposures associated with human activity will be primarily low-dose radiation from medical tests, waste cleanup, terrorism (“dirty” bombs), and environmental isolation of materials associated with nuclear weapons and nuclear power production.

Normal annual exposure from natural radiation (0.3 centigray per year)	
Radon gas	0.20 centigray
Human body	0.40 centigray
Rocks, soil	0.28 centigray
Cosmic rays	0.27 centigray
Normal annual exposure from human-made radiation (0.07 centigray per year)	
Medical procedures	0.0053 centigray
Consumer products	0.0010 centigray
One coast-to-coast airplane flight	0.0002 centigray
Watching color TV	0.0001 centigray
Sleeping with another person	0.0001 centigray
Weapons test fallout	>0.0001 centigray
Nuclear industry	>0.0001 centigray

The chart above shows sources of ionizing radiation from both natural and human sources.

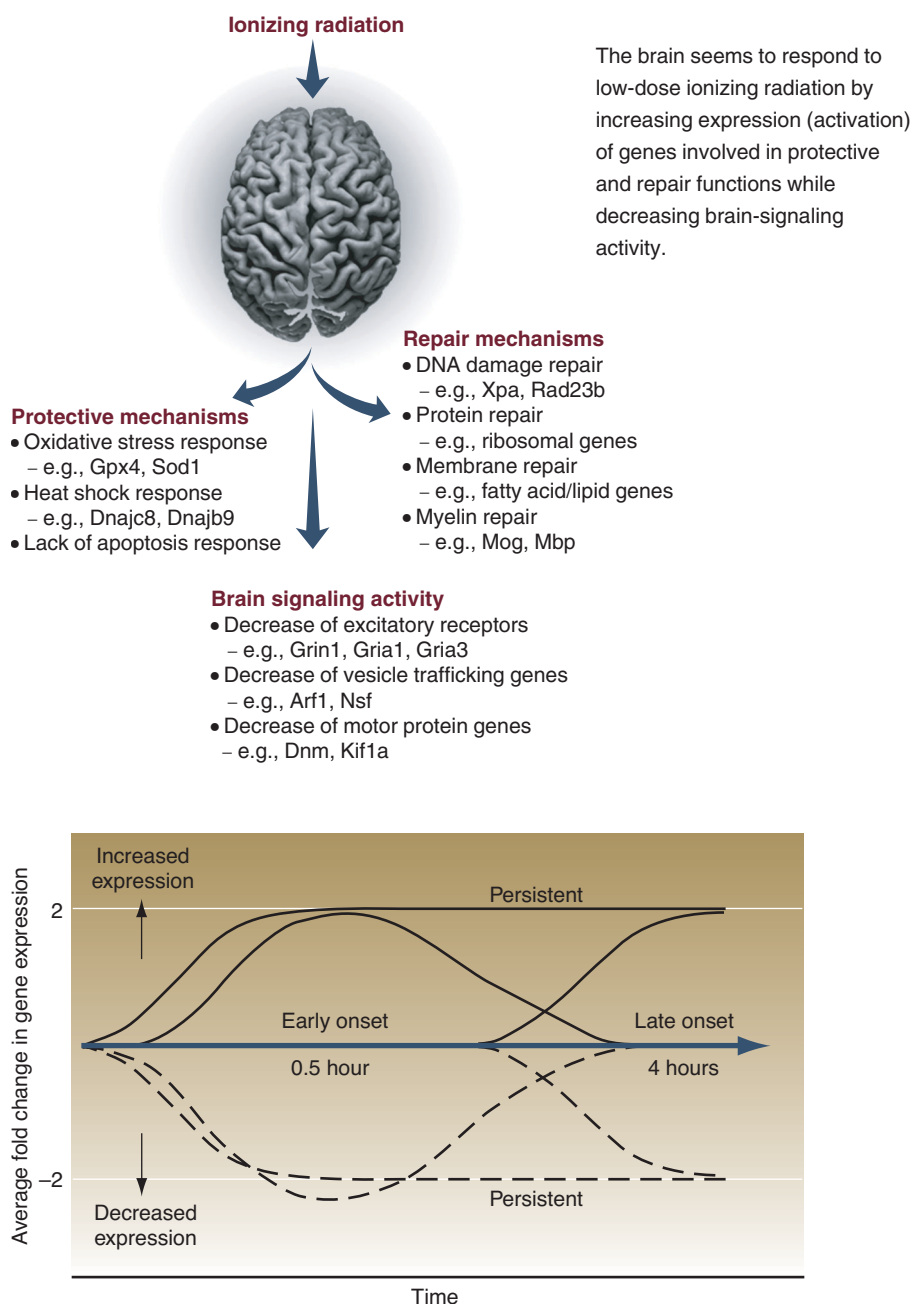
Wyrobek points out that different tissues are expected to respond differently to ionizing radiation. In an experiment of unirradiated tissues, 27 percent of 417 genes represented on a microarray were differentially expressed among five tissues (testis, brain, liver, spleen, and heart). The expression of the DNA repair genes was the least variable among the tissues, while genes responsible for coping with general stress show much greater variability.

### Low-Dose Exposure Can Protect

The team also discovered that the human lymphoblastoid cells exhibit what is called an adaptive response to ionizing radiation. An extremely low dose (also called a priming dose) appears to offer protection to the cell from a subsequent high dose (2 grays) of ionizing radiation. The degree of protection was measured by the amount of reduced chromosomal damage. A priming dose of 0.05 gray, administered about 6 hours before the high dose, can reduce chromosomal damage by 20 to 50 percent, compared with damage to cells that were not exposed to the priming dose.

“Pretreatment with a low dose of ionizing radiation sets the cell up to better survive a much higher dose of radiation. A tiny stress apparently helps a cell get ready for a bigger stress,” says Coleman. About 200 genes were found to be associated with adaptive response in the human lymphoblastoid cells. Of these, about half were turned on, and half were turned off. “We want to know what genes and pathways are associated with adaptation. Is the adaptive response similar to the low-dose response? We don’t yet know.”

Coleman says that adaptive responses were first reported in the early 1980s, although many scientists doubted the accuracy of the reports. “Now people are saying this effect happens throughout nature, including in plants. Regulatory agencies are convinced these effects do



Exposure of the mouse brain to ionizing radiation induces time-dependent changes in gene-transcript (mRNA) expression. Genes associated with specific biological functions show several distinct patterns of radiation response: early-onset and transient, late-onset, and persistent over time. Genes associated with ion regulation and control of gene expression showed early-onset and transient changes. Genes associated with radiation protection (for example, heat shock, oxidative stress) and synaptic signaling showed early onset with both transient and persistent patterns. Genes associated with cellular repair (for example, myelin, protein synthesis) showed late-onset changes in expression.



happen and that they may play a role in human health.”

### Proteins Provide More Clues

The team is also looking for protein changes in irradiated cells. “Proteins give us a more complete picture of cell response to radiation,” says Coleman. However, proteins are more difficult to work with than mRNA because of their instability and many modified forms. “They can go through many reactions that make them active or inactive.”

The researchers are using a number of techniques to identify radiation-induced

proteins. They are collaborating with colleagues at Livermore and Pacific Northwest Laboratory in using specialized mass spectrometers to gain a better understanding of the proteins. So far, the spectrometers have shown that two proteins, as yet unidentified, seem to be produced in large quantities only in response to high-dose ionizing radiation and are produced in much lower quantities in response to low-dose ionizing radiation.

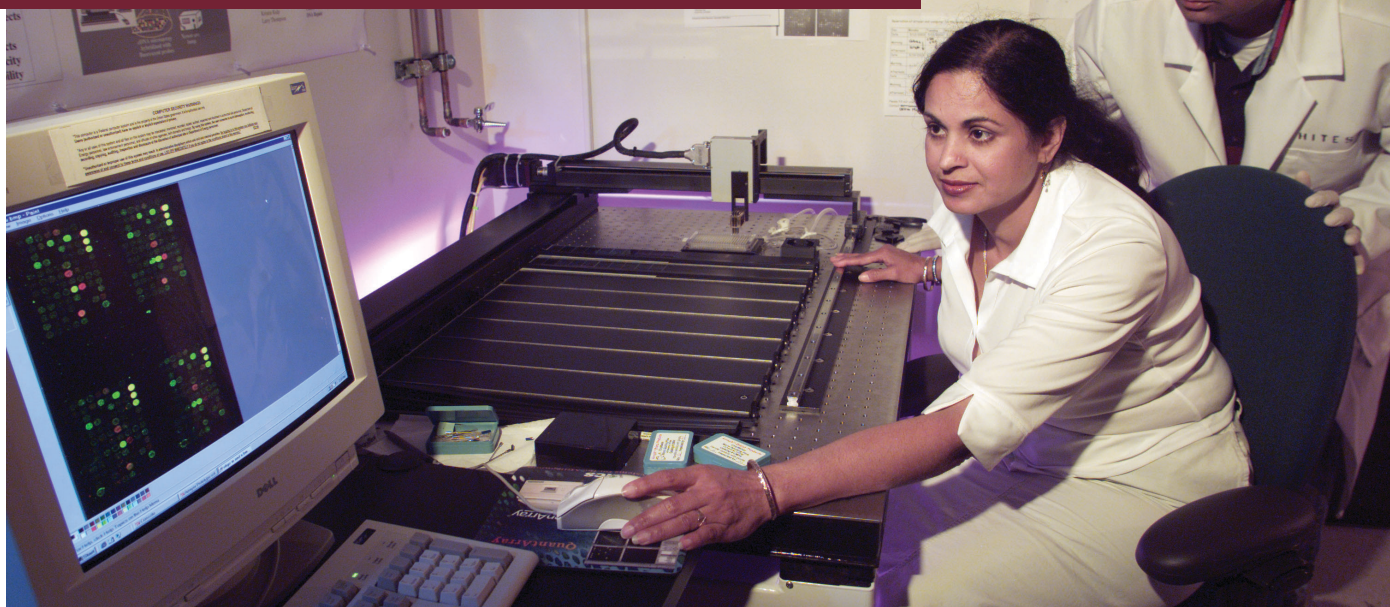
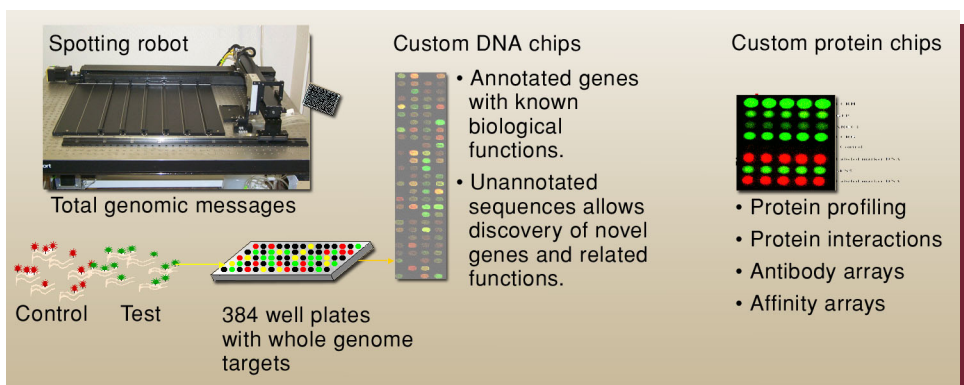
The team is also using two-dimensional gel electrophoresis, an old and more established technique, to

separate and identify proteins. This technology works by separating proteins by their size and electrical charge.

The researchers have also begun using protein microarrays, which work in a similar manner to DNA microarrays. The value of this technique is limited, however, because users must know in advance what proteins they are trying to find.

### More Work Ahead

Much work lies ahead. “We still have to show exactly what cell mechanisms and pathways come into play. We need to identify the genes that are expressed in association with a low-dose ionizing radiation exposure and those that are expressed for adaptive response,” says Wyrobek. The team also needs to better



Researcher Chitra Manohar shows colleague Hitesh Kapur the analytical results of changes in gene expression of tens of thousands of genes examined by microarray technology. The microarrays are on the spotting robot to the right of the computer screen. Livermore has developed customized microarrays for analyzing specific sequences of DNA and proteins (see inset).



understand the differences among tissues and how these relate to the risk of acute radiation sickness and long-term health effects.

The DOE low-dose program is also preparing to study low-dose response from other chemical and microbial toxins. "These radiation effects studies are setting the stage for modern molecular toxicology of cells and tissues," says Wyrobek.

"Radiation is just one kind of toxic material that damages chromosomes and kills cells. Does a cell respond in like manner to toxic chemicals, bacterial toxins, or even to cell toxicity caused by bacteria or viral infections? We don't know. We do know that some of the genes involved in cell response to low-dose ionizing radiation are the same ones that respond to chemical stress and to viral and bacterial infection." The answers to all the radiation-response questions may have a huge effect on understanding whether high doses of a suspected toxic chemical on laboratory animals are relevant to humans ingesting the same material but in much smaller doses.

Another worthwhile avenue of research is determining if individual genetic differences exist that render some people more or less sensitive to ionizing radiation. Wyrobek notes also that the Livermore experimental findings are based on the aggregates of millions of cells. "It is possible, for example, that just one or only a few types of cells within a tissue can respond differently

to ionizing radiation. We already know that cells in tissues differ dramatically in their sensitivity to cell killing, but we know little about the underlying molecular mechanisms. Determining the differential response of cells in tissues to insult is an important next step of research."

An important new research tool available to Livermore researchers is a nanoscale dynamic secondary-ion mass spectrometer (NanoSIMS). This instrument is only the second such machine in the nation dedicated to biological research. It can scan a tissue and identify the regions where a selected gene is expressed. (See p. 18 of the previous article for a discussion of NanoSIMS used for quantitative imaging of biological materials.)

Wyrobek says the experimental findings are relevant to homeland security and for assessing biological dose after incidents of chemical and biological warfare and so-called dirty radiological bombs. Whenever there is a suspected exposure incident,

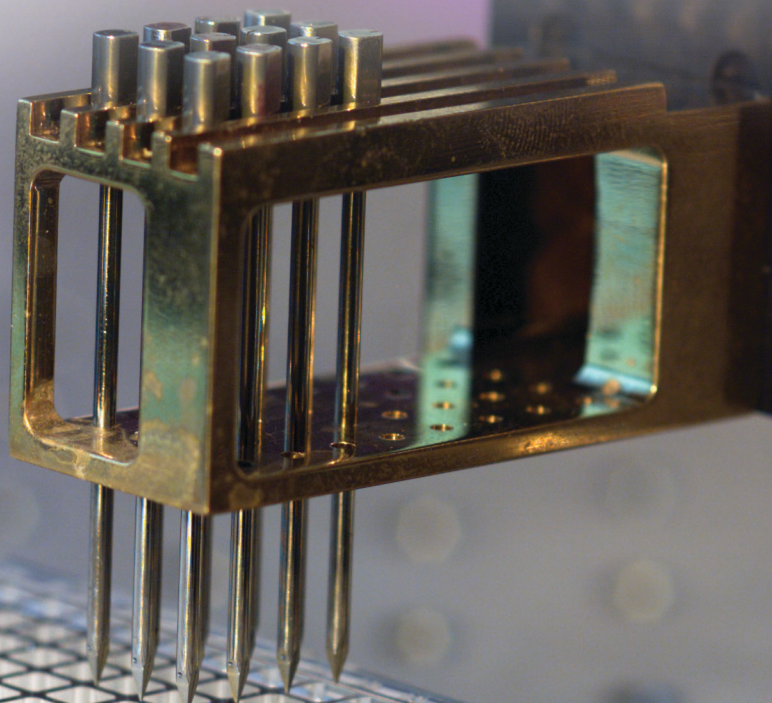
investigators will always have to try to determine exposure dose and assess health effects.

He notes that it is too early to tell if exposure standards will be changed as a result of the work funded by the DOE low-dose program. "We know a lot of things are going on at the low-dose level. What they all mean in terms of health is uncertain," says Wyrobek. But the new knowledge will certainly help ensure that the existing standards are appropriate. At the very least, he says, "We should no longer assume that cells respond in a linear fashion to exposure to ionizing radiation."

—Arnie Heller

**Key Words:** DNA, human lymphoblastoid cells, ionizing radiation, Low-Dose Radiation Research Program, messenger RNA (mRNA), nanoscale dynamic secondary ion mass spectrometer (NanoSIMS), radiation-induced early-onset and sensitive genes (REOS).

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# A New Generation of Munitions

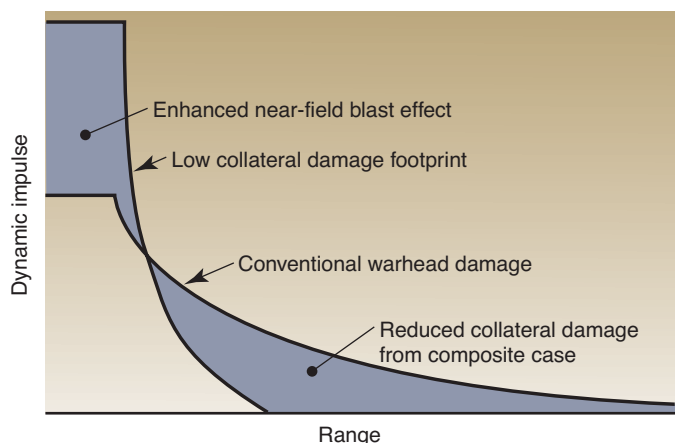
**A**S the conflict in Iraq unfolded this spring, the world watched in amazement at the accuracy of the latest generation of precision-guided missiles. These weapons allowed U.S. and allied air forces to operate unconstrained by the limits of daylight, and they came to “rule the night.” Now, the U.S. armed forces want to further extend this weapon capability by developing armament that will reduce collateral damage—that is, reduce destruction outside the radius of an intended target—while enhancing its destructive force on the target.

To achieve this goal, explosives and composites experts at Lawrence Livermore are leading an effort under a memorandum of understanding (MOU) between the Department of Energy

and the Department of Defense that was formalized in 1985. The MOU established a joint munitions program that takes advantage of the Laboratory’s expertise in high explosives, computer simulation, and other technologies. In the present effort, a Livermore team led by engineer Michael Murphy is working in partnership with the Air Force Research Laboratory at Eglin Air Force Base in Florida and the Naval Surface Warfare Center in Dahlgren, Virginia. The team is developing munitions with carbon-composite casings filled with new formulations of a high explosive that will greatly reduce damage to objects beyond the intended target.

Livermore researchers have studied high explosives for decades as part of their work in designing nuclear weapons. The Laboratory is the first to design a carbon-composite cased munition with an enhanced-blast-formulation explosive. “Much of the weight in today’s munitions is in the steel casing,” explains Murphy. “The heavy steel case, coupled with a high explosive, can penetrate hard targets such as reinforced concrete bunkers. However, the blast created by conventional steel-cased munitions can send shrapnel to distances of more than 1 kilometer from the target. This puts civilians and friendly forces at risk. We’re trying to change that by developing carbon-cased munitions with penetration capability.”

The challenge for the Livermore team was to design a munition that could penetrate hard targets as deeply as a steel-cased munition while restraining the energy of the blast within a small radius. Murphy notes, “If you could get the job done without throwing all that steel around, you would reduce collateral damage. It is a matter of controlling the energy and putting it to better use.” Carbon composite is lightweight, and the weight of the carbon-composite case will account for only 10 to 20 percent of a munition’s total weight. The Livermore team working on the composite-case design and fabrication technology is led by engineer Scott Groves.



The new munition is designed with an enhanced-blast explosive, which increases the impulse delivered to the intended target, and a carbon-fiber composite case, which eliminates collateral damage caused by case fragments. The graph shows that even though the new munition produces a more powerful blast, the range of its damage footprint is smaller than that of conventional warheads.

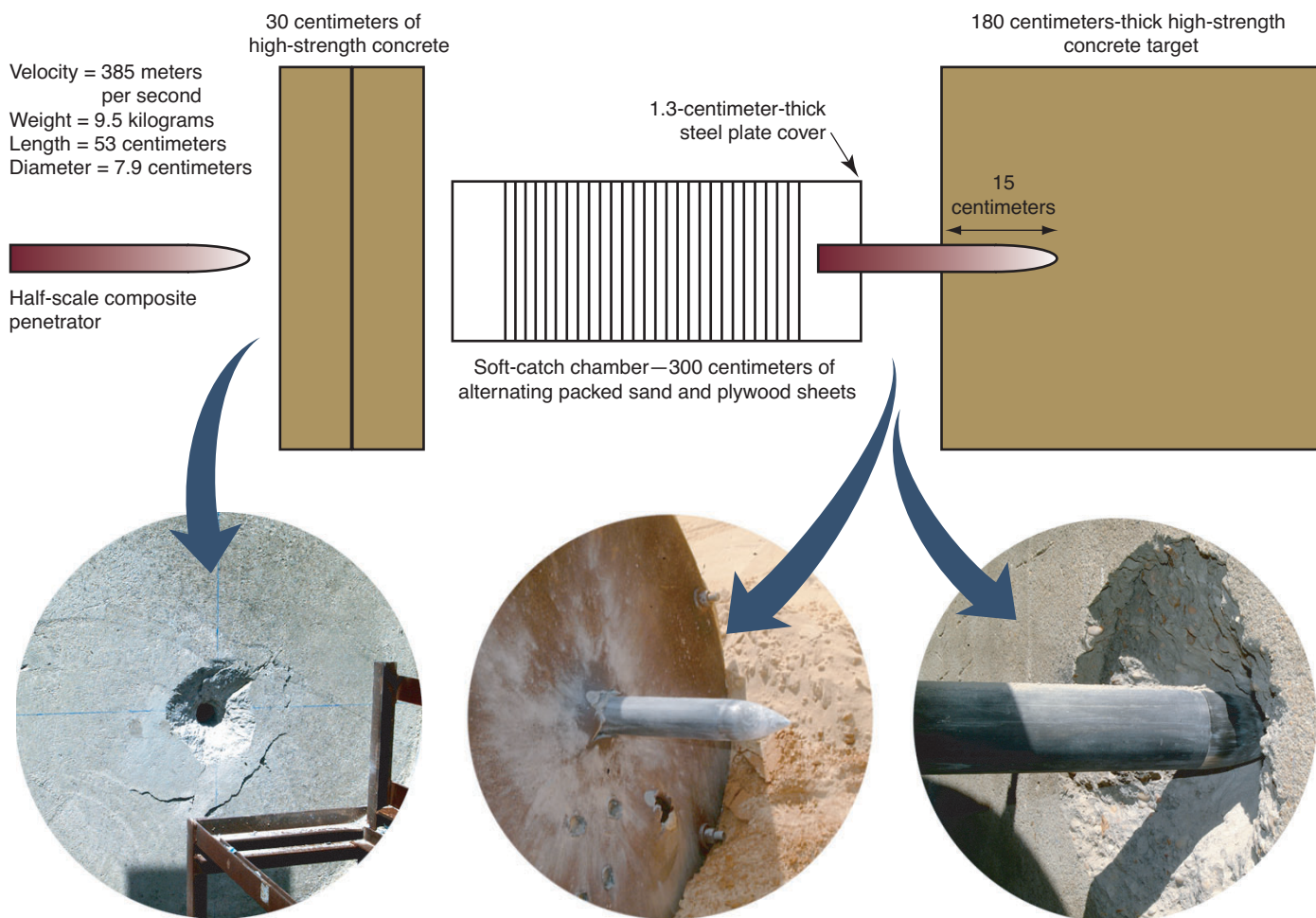


The first question facing the researchers was whether a composite case could penetrate concrete as deeply as its steel counterpart. In experiments conducted by Don Cunard at Eglin, Groves's team demonstrated that it could. The steel-nosed composite penetrator used in the experiments is a half-scale construction of the one used by the military. Shot at a velocity of 494 meters per second, it reached a penetration depth of 48 centimeters, far exceeding the penetration goal of 15 centimeters. In another test (see [figure](#) below), a penetrator traveled through 30 centimeters of concrete, 300 centimeters of sand and plywood, a 1.3-centimeter-thick steel cover plate, and another 15 centimeters of concrete, for a total distance of 3.3 meters. One advantage of the composite case, Groves

surmises, is that it may be more slippery than steel, which results in less friction against concrete.

### Balancing Destruction and Safety

To enhance the energy delivered to a target while also controlling the radius of the damage area, Livermore researchers Randy Simpson, Mark Hoffman, Roz Swansiger, Wardell Black, Rob Schmidt, and A. J. Boegel are formulating and testing a triamino-trinitrobenzene- (TATB-) enhanced explosive. TATB has long been used at Livermore because it is a powerful explosive that is also very insensitive; that is, it is highly unlikely to explode accidentally. At the same time, the Air Force is developing an enhanced-blast explosive with



Experiments conducted at half-scale demonstrate the ability of the carbon-fiber-cased projectile to survive the penetration through a target consisting of high-strength concrete, packed sand and wood, and steel. The lower part of the figure shows that the projectile survived intact while penetrating through the multilayer target. It penetrated deeper than expected and was not stopped by the soft-catch chamber of sand and wood.

cyclotetramethylene-tetranitramine (HMX). HMX delivers more energy than TATB, but it is also far more sensitive. "It's a tradeoff between safety and energy," says Murphy. "Weapons need to be powerful enough to do the job but safe enough so they are not vulnerable to accidents during transportation."

### Testing the Enhanced Formulas

To test the new TATB-enhanced formulation, researchers conducted static detonation experiments to measure the radius of the blast created. The goal was to deliver the most damage at close range, while leaving objects at a distance intact. In one test conducted at the Air Force Research Laboratory, insulating foam bundles were placed at distances of 2 meters, 3 meters, and 5 meters from the charge as a method of collecting the resulting case fragments. The foam bundle at the 2-meter range was obliterated while the foam bundles at the 3- and 5-meter distances had no case fragment penetrations and thus were unscathed. The few carbon case fragments that were recovered at the 2-meter range measured less than 1 centimeter each; no fragments were recovered beyond this distance. The Livermore team and its Air Force and Navy partners are strongly encouraged by the results.

The explosive fill in the munitions is fabricated from a mixture that has the consistency of toothpaste. The mixture is cast into the carbon-fiber case and cured. This process allows the munitions to be created in a variety of shapes for use in many different applications. The munitions created with the new technology will look and feel the same as those in use today, so they can be used with existing weapons. Aerojet, the company that builds the rocket boosters for the U.S. space program, is fabricating the composite munition case.

Murphy, along with Livermore researchers Estelle McGuire and Jack Reaugh, is also conducting simulations of the target penetration and detonation experiments to predict the warhead's physical and timing parameters, such as velocity,

pressure, and energy delivery. The simulations are performed using DYNA2D, CALE, ALE3D, and CHEETAH, computer simulation programs developed at Livermore. The results produced by these simulations reflect differences in timing and behavior between conventional steel-cased, high-explosive munitions used today and the unique design of the carbon-composite casing with the enhanced-blast explosive.

### Creating Tailored Warheads

Murphy believes that with adequate funding, the new composite-cased TATB-enhanced-blast munitions can be ready in six months to a year. The Livermore team is developing munitions for a few specific applications that have been requested by the Air Force. These munitions can easily be tailored to other applications as well. "If we develop something that looks interesting, someone will provide the funding for us to make it. Because of recent military activities in Iraq and Afghanistan, some of our armament resources are depleted and have to be replenished. Now is a good time to bring in the newer technology," says Murphy.

One of the current goals of military operations is achieved through the ability of U.S. armed forces to reliably hit and destroy their targets while minimizing collateral damage. In addition to providing more safety to soldiers and civilians on the ground, the new, low collateral damage munitions will also minimize the rebuilding that is needed after a war. The Air Force-Navy-Livermore team is excited about these promising advancements that will bring low collateral damage munitions to the next generation of armament technology.

—Gabriele Rennie

**Key Words:** ALE3D, CALE, carbon composite, CHEETAH, collateral damage, DYNA2D, HMX, munitions, TATB.

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# Whatever the Waste, New Facility Takes It On

**F**ROM a 19-kiloliter tanker truckload of wash water to a test-tube-size container of an unusual blend of noxious chemicals, Lawrence Livermore's new Decontamination and Waste Treatment Facility (DWTF) will take it all, fulfilling its role of helping the Laboratory keep "clean" when it comes to waste.

DWTF is a new, integrated facility for storing and processing the Laboratory's wastes, whether they be hazardous, low-level radioactive, transuranic radioactive, or mixed (that is, both chemically hazardous and radioactive). More than 20 years in the making, DWTF is scheduled to open by the end of September 2003. According to Stephanie Goodwin, division leader for Radiological and Hazardous Waste Management, DWTF will provide safe, cost-effective waste operations and will broaden Livermore's overall internal waste management capabilities. "Our role is to develop and improve ways of managing wastes generated at the Laboratory to ensure that the environmental impact of by-products is as negligible as possible," she says. "To that end, we first investigate and then

design, develop, and acquire new, more efficient ways to handle, stabilize, treat, certify, and dispose of waste. DWTF is key to all those efforts."

## Facility Does It All

Unlike a commercial industry that turns out widgets and produces the same kinds of waste streams in basically the same quantities day after day, Lawrence Livermore's unusual and diverse research and development activities generate comparatively small quantities of waste of widely varying composition. Waste Treatment group leader John Bowers explains, "For example, we get sink drainings, water cuttings, wax that has been stripped off floors of buildings where radioactive materials are used, and contaminated water from the Contained Firing Facility at Site 300 [Livermore's high-explosives research facility]." Those waste streams and others can contain alpha, beta, and gamma particles and emitters, as well as organic constituents such as oils and solvents, and even



Many of the systems in the Decontamination and Waste Treatment Facility are computer controlled, including the off-gas system, the evaporator, and the tank farm. Here, engineer John Fitzpatrick is shown by the portable operating interface for the liquid waste processing area. In the background at left is the tank farm's central control panel, which shows the conditions of all tanks—how full they are, their temperature, pH, conductivity, and oxidation and reduction potential—and the status of pumps and valves. Every 20 milliseconds, the computer program reads all inputs and outputs and updates the color coding on the panel, providing real-time feedback on the systems.



heavy and transition metals. “It can be a real diverse brew,” he concludes. “We’ve got to be ready to deal with all of these waste streams in ways that protect human health and environment and comply with standards, orders, and regulations. DWTF was designed from the start to do this very job.”

The new facility is actually a complex of buildings that includes new indoor storage areas and a California-permitted treatment plant—all connected to an impressive ventilation system. For treating wastes, there’s a 2,200-square-meter building for processing solid waste while liquid waste is processed in a 1,600-square-meter building. “An important goal in processing is to reduce the volume of waste,” says chemical engineer Dave Larsen. “Since most waste disposal sites charge by volume, not mass, we do everything we can to compact and reduce waste volume, both solid and liquid.” So liquid wastes are evaporated—resulting in water, suitable for

sending down a sewer, and a much-reduced solidified secondary waste. Solid wastes generated at Livermore are shredded to further squeeze down their volume.

The solid-waste processing building is equipped with two 4.5-metric-ton bridge cranes that can move large items, drum crushers that can mash drums of all sizes into flat pancakes, and a transuranic waste repackaging glovebox that can be used to open, repack, segregate, and ready for disposal the contents of 55-gallon (200-liter) waste drums.

The centerpiece of the liquid waste processing building is an enormous enclosed “tank farm” with nine 17-kiloliter, closed-top tanks, an arrangement that offers many advantages over the previous open-air tank farm, which has six open-top 5.5-kiloliter treatment tanks and four 17-kiloliter storage tanks. Reagents are delivered directly into the new tank farm using an integrated system.

The advantages of the new system are that the tanks are larger and off gases generated during treatment can themselves be treated, an option that wasn’t available in the old facility. Additionally, DWTF offers greater control through an enhanced programmable logic control system. More monitoring is available through augmented sensors, and waste streams are more segregated through the additional tanks and isolation plumbing. DWTF’s liquid-processing building includes a process development laboratory that can be used for treatability studies, process verification, and small-scale treatment. The building also includes gloveboxes, fume hoods, and a high-ventilation room to process reactive and highly toxic materials.

The solid- and liquid-processing buildings share a ventilation system designed to control the direction of air flow throughout the facility. “With all doors closed and the facility ventilation system functioning normally,” says Larsen, “there is a difference of 0.03 in water-gauge pressure between zones. When the roll-up doors are opened to let a truck into the truck bay, for instance, the pressure differential falls dramatically, but the air flow direction is still into the building, not out.”

All the air in the two buildings is fed through enormous banks of high-efficiency particulate air (HEPA) filters—over 90 of them—before it goes out the stacks. “We monitor what goes out the stacks and make sure it meets all standards,” notes Bowers. Even the choppers and shredders have their own HEPA filters. Air is filtered first at the stations before being sucked into the building’s ventilation system and filtered again at the main HEPA filter banks. A similar process occurs in the tank farm, where the gases and vapors that accumulate in the tanks are routed to a special process off-gas system that scrubs the gas and uses carbon adsorption to eliminate acid gas and organic vapor. The end result of having an integrated ventilation system and operations performed in

## Glossary of Radiological and Hazardous Waste

**Hazardous waste:** Waste that can pose a substantial or potential hazard to human health or the environment when improperly managed. It possesses at least one of four characteristics—ignitability, corrosivity, reactivity, or toxicity—or appears on special Environmental Protection Agency lists.

**High-level waste:** Radioactive waste that results from the reprocessing of spent fuel elements from nuclear reactors. It also includes reprocessed military wastes, such as sludges.

**Low-level waste:** A general term for a wide range of wastes having low levels of radioactivity. Low-level waste is radioactively contaminated industrial or research waste such as paper, rags, plastic bags, protective clothing, cardboard, packaging material, organic fluids, and water-treatment residues. Low-level wastes containing source, special nuclear, or by-product material are acceptable for disposal in a land disposal facility.

**Mixed waste:** This waste contains a hazardous waste component and a radioactive material component. Examples include liquid scintillation cocktails; corrosive organics; waste oils; and cleaning, degreasing, and miscellaneous solvents, which are also radioactive.

**Transuranic waste:** Transuranic refers to atoms of synthetic elements that are heavier (higher in atomic number) than uranium. Transuranic waste materials have been generated in the U.S. since the 1940s, mostly from nuclear weapons production facilities for defense programs. The most prominent element in most transuranic waste is plutonium. Some transuranic waste consists of items such as rags, tools, and laboratory equipment contaminated with radioactive materials. Other forms of transuranic waste include organic and inorganic residues or even entire enclosed contaminated cases in which radioactive materials were handled.

enclosed spaces is that the public, the workers, and the environment are all protected.

### Dealing with the Unusual

DWTF uses conventional, tried-and-true techniques and technologies such as evaporation to treat wastes as simply as possible, whenever possible.

Yet, with the Laboratory being what it is, DWTF and its people need to be ready to take care of waste streams that, as environmental engineer Dianne Gates-Anderson explains, are unique and unusual and require individual attention and specialized treatment. Such as those aforementioned HEPA filters. HEPA filters are designed to remove at least 99.97 percent of airborne particles with diameters greater than or equal to 0.3 micrometers. Eventually, a HEPA filter traps so many particles that it no longer can hold any more and must be replaced. In many cases, these spent HEPA filters are highly contaminated and must be treated.

Gates-Anderson says, "We generate a lot of spent HEPA filters at the Laboratory that require treatment before offsite disposal. The Laboratory has also been storing old legacy HEPA filters, such as those used in gloveboxes, that are often defined as mixed waste because they are contaminated with both radioactive and hazardous constituents."

These mixed-waste filters didn't have a lot of attractive treatment alternatives—until Gates-Anderson and a team of waste treatment engineers and technicians developed the patented In Situ Stabilization and Filter Encapsulation

(IS\*SAFE) process. This process uses a commercially available resin that has a waterlike consistency for 3 hours before it turns solid. A vacuum pump sucks the watery resin into the spent filter, and the resin fills the interior of the filter, sealing contaminants in place. Once the resin hardens, the contaminants cannot be removed. The resulting encapsulated HEPA filter, if originally classified as a mixed waste, is now considered low-level waste and can be disposed of in a regulated waste disposal site. This reclassification is significant because low-level waste disposal costs are approximately 10 times cheaper than mixed-waste disposal costs.

Gates-Anderson notes that the IS\*SAFE process has many advantages over previous treatments. The most important advantage is that it's safe for workers and easy to use. "Workers don't have to destroy, shred, or dismantle the filter," she points out. "Any time workers handle waste less, worker safety is increased." Another advantage is that IS\*SAFE doesn't generate a secondary waste stream. There's no off-gassing, very little heat generated during curing, and the process can be used on older wood-frame HEPA filters and newer stainless-steel ones. "The IS\*SAFE process shows how a complicated problem can be solved without a complicated solution," says Gates-Anderson.

A second example of a simple, innovative solution for problematic waste streams involves depleted uranium waste. Uranium is a highly reactive metal that oxidizes (burns) easily—sometimes even igniting spontaneously (a quality



The Decontamination and Waste Treatment Facility's (DWTF's) process off-gas system does double duty removing acid and organic gases and vapors from off-gases generated throughout the facility. In the scrubber (the column to the left) off-gases pass over a hydroxide solution, which neutralizes any acid vapors and traps them in the basin at the bottom of the scrubber. The large tank in the middle holds a pair of carbon adsorption columns that trap organic vapors. Once the off-gas has been scrubbed clean, it passes through DWTF's central ventilation system and its banks of high-efficiency particulate air filters for a last scrubbing before exiting through the facility's stacks.

defined as pyrophoric). Pyrophoric depleted-uranium wastes are typically placed in steel drums and covered with liquid prior to storage. In addition to being radioactive and reactive, uranium metal is also chemically toxic at high concentrations. The Laboratory has an inventory of about 11,700 kilograms of pyrophoric depleted uranium. “No disposal facility will accept pyrophoric depleted uranium,” says Gates-Anderson, “so our goal was to find a way to convert this waste to something nonpyrophoric that would be accepted at a low-level radioactive waste disposal facility. We can’t make uranium disappear, but we can make it safe for disposal.”

Gates-Anderson headed a three-year Laboratory Directed Research and Development project to find a way to make uranium safe for disposal. Her team developed a three-step process of pretreatment, chemical dissolution with acid, and stabilization of the dissolution products. Their research focused on the second step—dissolving the solid uranium metal, which usually involves using a variety of nasty acids. “Since we have a sizable amount of depleted uranium to deal with, we didn’t want a process that would generate even more waste that we would have to dispose of in turn,” she explains.

The team explored the possibilities of using a number of reagents singly and in combination, including hydrochloric, sulfuric, and phosphoric acids as well as sodium hypochlorite, sodium hydroxide, and hydrogen peroxide. They zeroed in on a combination of hydrochloric and phosphoric acids. The process yields a semisolid uranium (IV) and phosphate compound, which is nonpyrophoric. “All we need to do at that point is neutralize its pH, solidify the material using conventional methods, and then we can dispose of the uranium as a low-level waste,” she says.

### Waste Away

There’s no way around the fact that a by-product of the Laboratory’s national security missions is an unusually diverse variety of wastes—some hazardous, some radioactive, some both. There is no magic wand one can wave to make this waste disappear or transform. But DWTF offers a realistic and responsible solution. Goodwin concludes, “The Laboratory has the responsibility to manage its waste from ‘cradle to grave.’ The researchers and scientists generate the waste in their work—the cradle—and here in our division we have to



Dianne Gates-Anderson holds a piece of encapsulated high-efficiency particulate air (HEPA) filter. The IS\*Safe process she and others developed encapsulates contaminants in used HEPA filters easily, safely, and without generating secondary waste as other processes do. This is good news for the DOE complex, which annually generates thousands of used HEPA filters that must be treated before disposal.

get it in the grave in ways that are safe, appropriate, and meet all regulatory requirements. DWTF enables the Hazardous Waste Management Division to better support the Laboratory’s programs and missions and to address community concerns with its environmental safety and health compliance.”

—Ann Parker

**Key Words:** Decontamination and Waste Treatment Facility (DWTF); depleted uranium; hazardous, radioactive, and mixed waste; In Situ Stabilization and Filter Encapsulation (IS\*SAFE).

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## Patents

### **Processing a Printed Wiring Board by Single Bath Electrodeposition**

**Michael P. Meltzer, Christopher P. Steffani, Ray A. Gonfiotti**

U.S. Patent 6,547,946 B2

April 15, 2003

A method of processing a printed wiring board by single bath electrodeposition. Initial processing steps are implemented on the printed wiring board. Then copper is plated on the board from a bath containing nickel and copper, followed by nickel plating on the board. The final processing steps are implemented on the printed wiring board.

### **Injector-Concentrator Electrodes for Microchannel Electrophoresis**

**Stefan P. Swierkowski**

U.S. Patent 6,558,523 B1

May 6, 2003

An input port geometry, with injector-concentrator electrodes, for a planar microchannel array for electrophoresis. The input port geometry enables efficient extraction and injection of a DNA sample from a single input port. It allows simultaneous concentration, in different channels, of the sample into a longitudinally narrow strip just before releasing it for a run with enhanced injection spatial resolution and time resolution. Optional multiple electrodes, at a different bias than that of the concentrator electrodes, may be used to discriminate against sample impurity ions. Electrode passivation can be used to prevent electrolysis. An additional electrode in or on the input hole can better define the initial loading. The injector-concentrator electrodes are positioned so that they cross the drift channel in a narrow strip at the bond plane between the top and bottom plates of the instrument and are located close to the inlet hole. The optional sample purification electrodes are located at a greater distance from the input hole than the injector-concentrator electrodes.

### **Conformal Chemically Resistant Coatings for Microflow Devices**

**James A. Folta, Mark Zdeblick**

U.S. Patent 6,562,404 B1

May 13, 2003

A process for coating the inside surfaces of silicon microflow devices, such as electrophoresis microchannels, with a low-stress, conformal silicon nitride film that has the ability to uniformly coat deeply recessed cavities with, for example, aspect ratios of up to 40:1 or higher. The silicon nitride coating allows extended exposure to caustic solutions. The coating enables a microflow device fabricated in silicon to be resistant to all classes of chemicals: acids, bases, and solvents. The process involves low-pressure (vacuum) chemical vapor deposition. The ultralow-stress silicon nitride deposition process allows 1- to 2-micrometer-thick films without cracks and so enables extended chemical protection of a silicon microflow device against caustics for up to a year. Tests have demonstrated the resistance of the films to caustic solutions at both ambient and elevated temperatures to 65°C.

### **Bistable Microvalve and Microcatheter System**

**Kirk Patrick Seward**

U.S. Patent 6,565,526 B2

May 20, 2003

A bistable microvalve of shape memory material is operatively connected to a microcatheter. The bistable microvalve includes a tip that can be closed off until it is in a desired position. Once it is in position, the bistable microvalve can be opened and closed with the use of heat and pressure. The shape memory material will change stiffness and shape when heated above a transition temperature. The shape memory material is adapted to move from a first shape to a second shape, either open or closed, where it can perform a desired function.

## Awards

During a ceremony at National Nuclear Security Administration headquarters in Washington, DC, NNSA Administrator Linton Brooks awarded the **Department of Energy Secretary's Gold Award** to **Bob Kuckuck**, former deputy director of Operations. The award is DOE's highest honor. In the award citation by Energy Secretary Spencer Abraham, Kuckuck was recognized for "superior leadership" and for "vision, dedication and commitment to excellence . . . that have directly resulted in the advancement of initiatives that are strengthening the nuclear security of the United States of America."

Kuckuck was appointed acting principal deputy administrator for NNSA in June 2001, shortly after he retired from the Laboratory. His NNSA assignment ended in December 2002, and he is currently a senior adviser to Bruce Darling, the University of California vice president of Laboratory Management.

The **Society for Technical Communications** has honored the Innovative Business and Information Services Department with three publications awards. It gave a **Distinguished** award in the annual report category to **Gloria Cannon, Ralph Jacobs**, and **John Danielson** for the *Physics and Advanced Technologies 2001 Annual Report*; an **Excellence** award in the magazine category to the **staff** of *Science & Technology Review*, publication sponsor **Tom Isaacs**, and scientific editor **Kimberly Budil**; and an **Excellence** award in the book category to **George Kitrinis, Pam MacGregor**, and **Paul Chrzanowski** for *Fifty Years of Accomplishments*, which was published to celebrate the Laboratory's 50th anniversary.

### An Inside Attack on Cancer

Livermore researchers are collaborating with scientists at the University of California at Davis Cancer Center to develop new methods to prevent, diagnose, and treat cancers that have metastasized. The goal of this work is to be able to deliver treatment that is specific to the needs of each patient. Specially designed molecules called high-affinity ligands can be tagged with a radionuclide to deliver deadly radiation to cancer cells. The beauty of this targeted radionuclide therapy is that diseased cells receive a much higher fraction of total dose than chemotherapy can deliver. The radioactive material destroys cancerous tissue while normal tissue stays healthy. A new gamma radiation detector will use similarly tagged molecules to reveal precisely where cancer cells are located to assist with diagnosis and treatment planning. Livermore and other partners are also developing a software tool called MINERVA for customized planning of targeted radionuclide therapy. Finally, to examine the specific effects that radionuclides have on cells, the team recently began using a novel form of mass spectrometry with unprecedented spatial resolution to examine the amounts of radioisotopes in cells.

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### Cells Respond Uniquely to Low-Dose Radiation

For the first time, research is showing that low-level ionizing radiation causes cells to respond by activating genes that specialize in repairing damaged chromosomes, membranes, and proteins and in countering cellular stress. The activity of these cells is not simply a reduced level of that seen in cells exposed to high doses of ionizing radiation. Rather, many genes are called into action in response only to low radiation doses. The Livermore research is conducted on laboratory mice and human cell cultures. The research also reveals an adaptive response in human cells, whereby a pretreatment of a tiny dose of ionizing radiation allows the cell to better withstand a later, much higher dose. The research further suggests that similar responses may be at work when a cell suffers low-level insults by harmful chemicals or is under attack by bacteria or viruses. The work is part of DOE's Low-Dose Radiation Research Program, which aims to determine any health risks from exposures to low levels of radiation. This information is critical to setting appropriate standards for exposure to low-level ionizing radiation, such as that received by medical tests, and to workers involved in such tasks as radioactive waste cleanup.

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## Livermore Commissions the National Ignition Facility



With only 4 of what will ultimately be 192 beams fully operational, the National Ignition Facility is already the most energetic laser in the world.

#### Also in September

- *Livermore scientists have developed two methods for monitoring how well hydrocarbon-loving bacteria can bioremediate gasoline-contaminated groundwater.*
- *Common buoys outfitted with radiation detectors could soon play an important role in safeguarding marine environments.*
- *A handheld radiation detector can duplicate the precision of laboratory spectrometers.*

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